Studies in 8-amino-6,7-benzomorphans.

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STUDIES IN 8-AMINO-6,7-BENZOMORPHANS

submitted by Shabir Hirani

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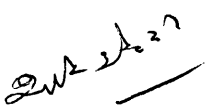

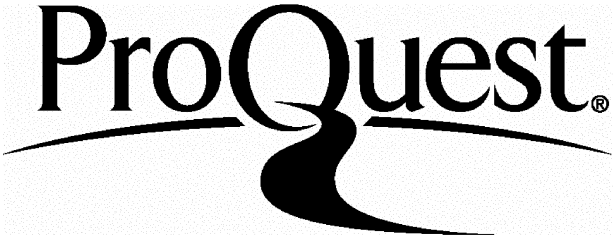

To my friend Lone.

"So many worlds, so much to do,
so little done, such things to be"

(A. Tennyson)

ACKNOWLEDGEMENTS

I owe an overwhelming debt to Professor R.T. Parfitt for his continuous encouragement, invaluable discussions and patient supervision throughout the course of this work. I have also had the advantage of discussions with Dr. G.H. Dewar who gave advice and suggestions of the greatest value.

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SUMMARY

This project involved the chemical modification of the 6,7-benzomorphan nucleus by introducing a second nitrogen pharmacophore at the benzylic position to give a series of 8-aminobenzomorphans with potential analgesic activity. Concise reviews of 6,7-benzomorphan, morphine and related analgesics, pertinent to this project together with background material are given in Part One of the thesis.

The introduction of oxygen at the benzylic carbon of the 6,7-benzomorphan in improved yields was achieved using dilute solution of chromium trioxide in acetic acid at room temperature. Various other oxidising agents which are known to attack benzylic methylene groups were also investigated and are reported in Chapter Two.

The stereoselective synthesis of the 8-amino-6,7-benzomorphan by reduction of the oxime is described. Catalytic hydrogenation of the oxime yielded 8α-aminobenzomorphan whereas LAH reduction gave the β-isomer. These reductions together with the various factors which influence the stereochemical course of reduction are discussed in Chapter Three. The relative configuration of 8-aminobenzomorphan was assigned on the basis of ^{1}H NMR studies. The stereochemistry of the 8β-aminobenzomorphan was confirmed by its successful cyclization via 8β-chloroacetamido-6,7-benzomorphan to the 2,8-bridged

benzomorphan derivative. All attempts to cyclize the 8α-chloroacetamide under similar conditions proved to be impossible as anticipated on steric grounds.

The 8α-cyanobenzomorphan obtained from 8-oxo-benzomorphan and tosylmethyl isocyanide was catalytically reduced to 8-aminomethyl-6,7-benzomorphan. Introduction of an aminomethyl group at the 8 position creates a second phenylethylamine moiety in the benzomorphan nucleus.

The stereochemistry of 8α-cyanobenzomorphan was determined from the ^{1}H NMR chemical shifts and coupling constant between C_1 and C_8 protons. Attempts to prepare the 8β-cyano compound by base-catalysed racemisation of the α-isomer surprisingly gave 8-oxobenzomorphan. A possible mechanism for this transformation is discussed in Chapter Five.

The availability of the nitrogen non-bonding electrons in the aminobenzomorphans was modified by acylation and alkylation. An unusual acylation reaction was observed for the 8β-amine and cyclopropanecarbonyl chloride in that it gave 8β-dicyclopropionamidobenzomorphan instead of the expected monoacylated derivative. A possible mechanism for this reaction is discussed in Chapter Three. Approach to the synthesis of 8-alkylaminobenzomorphan via reductive amination of 8-oxobenzomorphan was

investigated and shown to be unsatisfactory.

^{1}H and ^{13}C NMR data for a series of 6,7-benzomorphan derivatives prepared in this work is presented and discussed in Chapter Six. These data are not only of importance for identification and differentiation but also valuable in the evidence they provide of the configuration and conformation of the various derivatives.

The experimental details of the syntheses of the aminobenzomorphans and their derivatives are given in Chapter Seven.

CONTENTS

		Page
Acknowledgements		III
Summary		IV
PART ONE	INTRODUCTION	1
CHAPTER ONE	BENZOMORPHANS AS ANALGESICS	2
1.0	Morphine and related analgesics	4
1.1	Morphinans	10
1.2	6,7-Benzomorphans	12
1.3	Opiate receptors	30
1.4	Chemistry of benzomorphanones	40
PART TWO	DISCUSSION	60
CHAPTER TWO	SYNTHESIS AND REACTIONS OF BENZOMORPHANONES	61
2.0	Introduction	62
2.1	Synthesis of 2,5-dimethyl-6,7-benzomorphan and 2,5,9-trimethyl-6,7-benzomorphan	64
2.2	Synthesis of 2,5-dimethyl-8-oxo-6,7-benzomorphan and 2,5,9-trimethyl-8-oxo-6,7-benzomorphan	66
2.3	Synthesis of 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime and 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime	76
2.4	The synthesis of 8-cyano-2,5-dimethyl-6,7-benzomorphan	83
2.5	Attempted synthesis of 2,5,9-trimethyl-8-bromo-6,7-benzomorphan	86

Page

CHAPTER THREE 8-AMINO-6,7-BENZOMORPHANS AND THEIR DERIVATIVES 88

3.0 Introduction 89

3.1 Stereoselective synthesis of the 8α- and 8β-amino-6,7-benzomorphans 91

3.2 Reactions of 8-amino-6,7-benzomorphans 105

CHAPTER FOUR SOME POTENTIAL LONG ACTING NARCOTIC ANALGESICS AND A NEW BRIDGED AMINOBENZOMORPHAN 126

4.0 Introduction 127

4.1 Synthesis of 8α- and 8β-chloroacetamido-6,7-benzomorphan and 8α-chloroacetamido-methyl-6,7-benzomorphan 129

4.2 Synthesis of a novel tetracyclic benzomorphan; 2,8 bridged benzomorphan derivative 137

CHAPTER FIVE 8-AMINOMETHYL-2,5-DIMETHYL-6,7-BENZOMROPHAN AND RELATED COMPOUNDS 145

5.0 Introduction

5.1 The oxidative decyanation of 8α-cyano-2,5-dimethyl-6,7-benzomorphan: an attempt to prepare 8β-cyanobenzomorphan 148

5.2 Preparation of 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan. Reaction of 8α-cyano-6,7-benzomorphan 154

Page

5.3 Some reactions of 8α-aminomethyl-6,7-benzomorphan 161

CHAPTER SIX STEREOCHEMICAL STUDIES OF 8-SUBSTITUTED 6,7-BENZOMORPHANS AND THEIR DERIVATIVES BY ^{1}H AND ^{13}C NMR SPECTROSCOPY 170

6.0 PMR studies 171

6.1 ^{13}C NMR studies 186

CHAPTER SEVEN EXPERIMENTAL 205

7.0 2,5-Dimethyl-6,7-benzomorphan, 2'hydroxy-2,5-dimethyl-6,7-benzomorphan and 2,5,9-trimethyl-6,7-benzomorphan 208

7.1 Ketones 209

7.2 Reactions of ketones 215

7.3 Primary amines 220

7.4 Amides 226

7.5 Secondary amines 240

References 249

PART ONE

INTRODUCTION

CHAPTER ONE

BENZOMORPHANS AS ANALGESICS

CHAPTER ONE

BENZOMORPHANS AS ANALGESICS

A widely recognized medical need exists for an analgesic useful in the long-term treatment of chronic pain that is both safe and effective, with minimum respiratory depression and dependence properties.

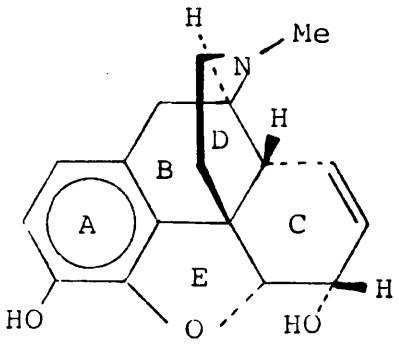
The oldest and best known analgesic is opium. For centuries the latex from the seed capsule of the opium poppy has provided pain relief unsurpassed by any other drug. Morphine, a major opium alkaloid, is still, in many cases, a preferred drug for pain relief. Its use, however, is restricted by its side effects, the most serious of which are respiratory depression, and development of tolerance and physiological and psychological dependence. In an attempt to overcome these side-effects, a considerable number of analogues of varying structure have been prepared, some of which have proved useful substitutes for morphine. Despite the substantial progress made, there remains a serious problem with analgesics in so far as analgesic, euphoric effects and dependence remain largely unseparated properties. Thus, the goal of an ideal analgesic still awaits achievement. Lack of knowledge of the fundamental physiology of pain and the subcellular mechanisms by which the analgesic drugs exert their pharmacological effects has hampered progress towards this goal. The pharmacological effects of opiates have been linked with interactions with the central nervous system neurotransmitters acetylcholine, dopamine,

noradrenaline, 5-hydroxytryptamine and substance P. The discovery of the opioid peptides now provides a new concept in the study and design of analgesic agents.

1.0 Morphine and related analgesics

The extract of the latex from opium poppy seed capsule is amongst the oldest materials employed for medicinal purposes, and the study of the major alkaloid in this extract, morphine (1), is one of the oldest areas of biological research. The Sumerians are thought to have used crude opium as early as 4000 B.C. for its ability to relieve pain and evoke a general feeling of peace and well being.

Morphine (1) was isolated from poppy latex by a German pharmacist, Sertuner, in 1803; since then twenty four other alkaloids have been isolated. The chemical structure of morphine was not fully understood until 1903 and was only confirmed in 1952 by synthesis[1].



(1)

Morphine produces a large variety of pharmacological responses, the most important of which are analgesia, euphoria, respiratory depression and dependence. It has a retarding action upon the digestive system and is an effective antidiarrhoeal agent. Its effect on depressing the cough reflex has been clinically utilized. But its principal effect has been in decreasing awareness and reaction to pain. The euphoric effects, and a reduction in anxiety and fatigue which are caused by it, is of importance in the alleviation of pain[2,3,4].

Unfortunately morphine use is accompanied by several serious side-effects which pose a major drawback to its exploitation. In particular the effect of morphine decreases with each successive dose; the presence of drug becomes more and more tolerated and progressively large doses are required for a given effect. After continued exposure to the drug, the body becomes dependent upon it for normal function. If the administration of the drug is terminated at this stage, severe withdrawal symptoms develop. The symptoms are generally opposite to the original effects of morphine and vary from stomach cramps, diarrhoea, sleeplessness, nervous excitation with dilated pupil, increase of respiratory rate to respiratory failure and ultimately death. The need for ever-increasing doses to maintain the analgesia and prevent withdrawal symptoms also increases the degree of side-effects such as nausea and constipation[2].

The mechanism involved in tolerance and physical

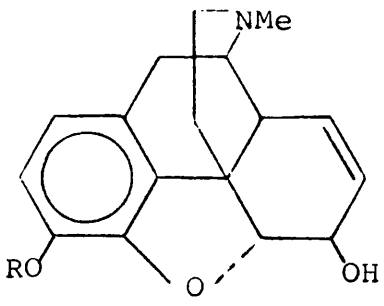
dependence remains largely unknown, in spite of intense biochemical investigation[5,6]. The hypothesis that tolerance is due to a change in the number or affinity of the receptors has been tested, but no such change was observed. Snyder [55] has proposed a model, in the light of the discovery of opioid peptides, which involves adenylate cyclase in the mechanism of analgesia, tolerance and physical dependence.

Respiratory depression is another undesirable effect and this depressant effect is the prime cause of death with higher doses. Other side-effects of morphine administration at therapeutic levels include antidiuresis, hyperglycemia, miosis, hypermotility, vomiting, nausea, mental confusion and depression of spinal reflexes. It also induces the release of pituitary hormone, prolactin and growth hormone. The pharmacology of morphine has been reviewed in detail[2,7].

Morphine is promptly absorbed after parenteral injection but absorbtion by the oral route is poor. It rapidly leaves the blood stream and is concentrated in parenchymatous tissue. The major pathway for metabolism of morphine is conjugation with glucuronic acid.

Numerous modifications of the morphine skeleton have been undertaken in an attempt to produce analgesia without morphine's harmful side-effects. Many morphine derivatives have been introduced in medical practice, some of which are very potent but they are all accompanied

by side-effects similar to morphine[8,9]. Codeine (2a), the phenolic ether of morphine, retains a useful degree of analgesic activity, and is widely used as an oral analgesic and antitussive agent. The abuse potential of codeine is lower than most other narcotic analgesics[10]. The ethyl (2b), benzyl (2c) and 4-morpholinoethyl (pholcodine, 2d) ethers have a similar clinical utility. Heroin, or diacetylmorphine (3), is more potent and shorter acting than morphine, but has a higher addiction liability. The pharmacological action of heroin is attributed to its hydrolysis products (6-monoacetyl morphine and morphine)[11].



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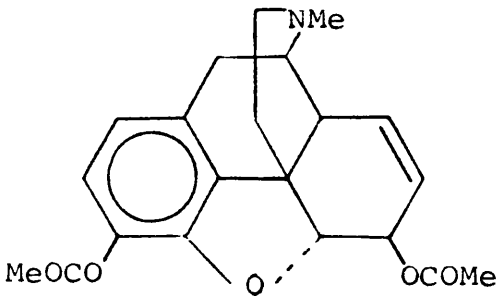


(3)

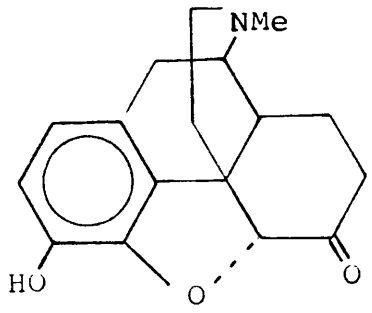
a) R = Me b) R = Et

c) R = CH_2PH

d) R = CH_2CH_2-N O

The chemical modification of ring C of morphine has led to several drugs that are clinically important[10]. These include dihydromorphinone (4), dihydromorphine (5) and Metopon (6). Metopon is about three times as potent as morphine and shows lower addiction liability but has not been promoted for general use. Desomorphine (7) is a fast acting, powerful analgesic with little emetic or gastrointestinal effects. The 14-hydroxy-7,8-dihydro compounds, oxymorphone (8a) and oxycodone (8b) are also marketed, and are very potent drugs. The 14-hydroxy derivatives, Naloxone (9a) and naltrexone (9b) are potent pure antagonists opposing the actions of morphine and are used for the treatment of narcotic analgesic overdose[11].

Many 6,14-endoethenotetrahydrothebaine derivatives (10) have extremely high potencies[12,13]. Etorphine (10, R=C_3H_7), for example, is 8600 times as active as morphine in guinea-pigs, and is used for immobilizing large animals for veterinary purposes and for game conservation. Diprenorphine (11, R=CH_3) is a potent antagonist with very little analgesic activity and is used for the reversal of etorphine actions. Buprenorphine[14] (11, R=t-Bu) is a very potent mixed antagonist - agonist (0.6mg≡15mg morphine) and has recently been introduced for a period of monitored clinical release in UK. It has a longer duration of action and produces a greater maximum analgesic effect than pentazocine.



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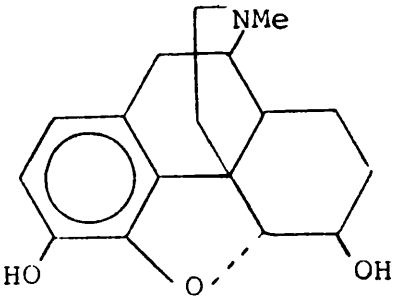

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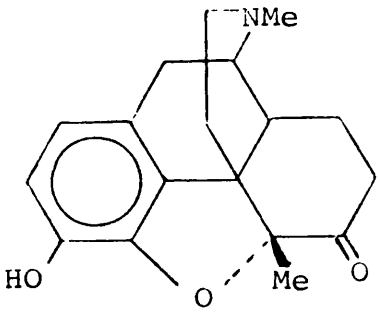

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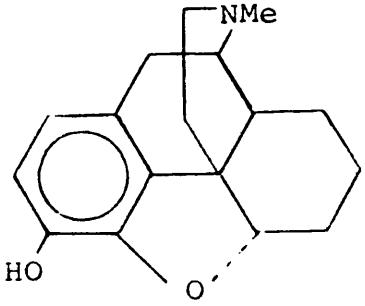

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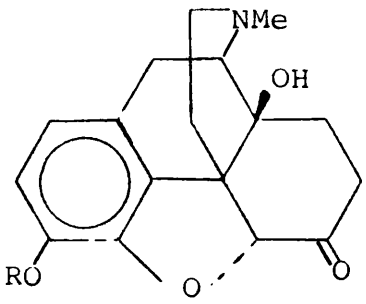

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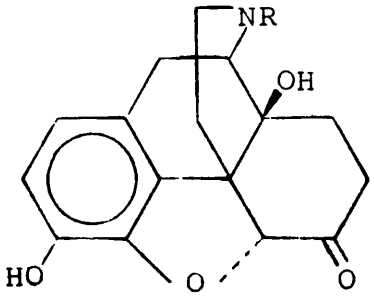


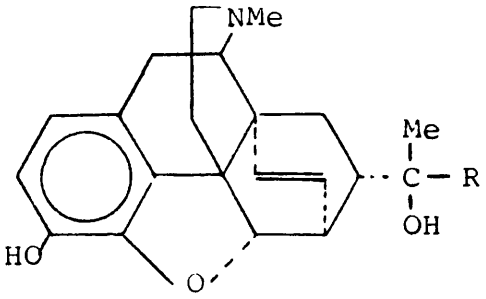
(9)

a) R = H

b) R = CH_3

a) R = $CH_2CH = CH_2$

b) R = CPM = Cyclopropylmethyl



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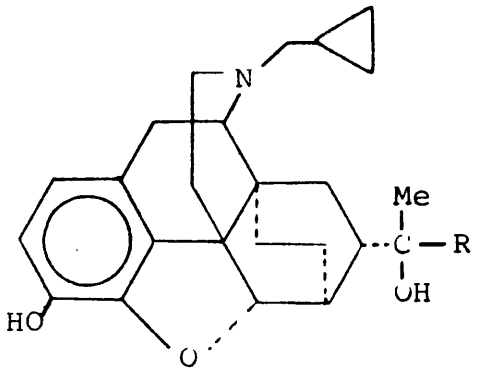


(11)

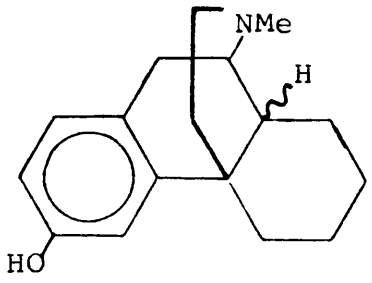
1.1 Morphinans.

Once the structure of morphine had been elucidated, attempts to synthesize it began. Among the early attempts at the total synthesis of morphine were those of the German chemist Rudolph Grewe[15]. From his investigations have evolved the morphinans(12), a class of compounds possessing the main structural skeleton of morphine (1) without 4,5-oxygen bridge. Schnider and Grussner[16] in 1949 and Grewe[17] soon after described racemorphan; (±)-3-hydroxy-N-methyl-morphinan (12) is an analgesic more potent than morphine with no greater harmful side-effects. The laevo enantiomorph (Levorphanol) which possesses the same absolute configuration as natural morphine was the form responsible for the analgesic activity.

Literally hundreds of morphinans have been evaluated for analgetic activity and acute toxicity, and some for

addiction liability and cough suppression. A complete review of these data has been published[18]. Although the side-effects in these compounds are not as severe as those found in morphine, all of them do show the deficiencies of the parent alkaloid (1) ie. its dependence liability and respiratory depressant properties.

Morphinan derivatives with 14-hydroxyl groups which cannot be obtained by the usual Grewe synthesis have been, recently, prepared by a novel procedure[19]. The N-cyclopropyl- and N-cyclobutyl/methyl derivatives (13a and b) represent two of the more interesting compounds to emerge from these studies.



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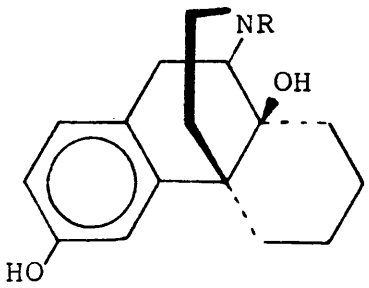


(13)

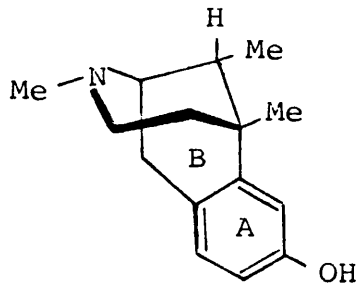
± Racemorphan

a) R = CPM

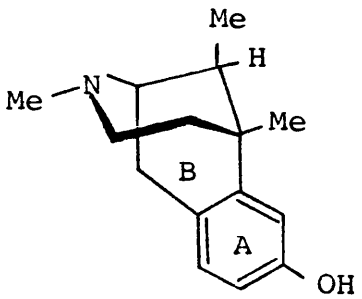
b) R = CBM = Cyclobutylmethyl

1.2 6,7-Benzomorphans.

The 6,7-benzomorphans are one of the most extensively investigated morphine analogues, first prepared and studied in detail by May and Eddy[20]. These compounds retain chemical features considered at one time essential for strong analgesic activity, namely an aromatic ring attached to a quaternary carbon atom and two carbon atoms removed from a tertiary amine function[21]. These compounds are essentially three ring segments of the morphine nucleus. The four possible diastereoisomeric forms resulting from asymmetry at C-1, C-9, and C-5 are reduced to two due to the cis B-C ring fusion. These two pairs are the α- and β-diastereoisomers which differ in configuration at C-9; in α-isomers 5,9-dialkyl substituents are cis with respect to the hydroaromatic ring B (14) while in β-form the groups are trans (15).



(14)



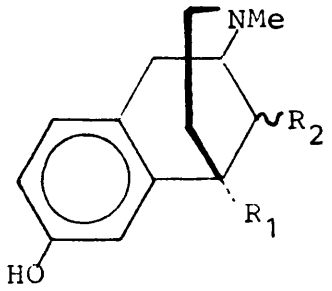
(15)

The stereochemistry of the 9-substituent was initially determined by the rate of quaternization[22] and by nuclear magnetic resonance (NMR) studies[23,93]. The rates of quaternization of α- are faster than those of β-isomers, the reaction in latter being hindered by the 9-alkyl group. The C-9 methyl in the α -isomer is upfield over 20 cycles from that of β and was interpreted in terms of a diamagnetic shielding of the α but not the β C-9 methyl by the fused benzene ring. The geometry of the 9 position has considerable influence upon the analgesic activity. Without exception, β-diastereomers are substantially more potent than the α-forms[22,24,25] in spite of their stereochemistry differing from that of morphine.

May and his colleagues[93], using a modified Grewe synthesis, prepared a number of 5-monoalkyl- and 5,9-dialkyl substituted benzomorphans, many of which possessed moderate to strong analgesic activity and low or no physical dependence capacity in monkeys. The influence of alkyl chain length at C_5 and C-9 upon activity differs somewhat in the diastereoisomers (Table 1). For example, the β-dipropyl derivative (16; R_1=R_2=Pr) is a potent analgesic whereas the corresponding α-isomer is essentially inactive.

The β derivatives with a C_5 ethyl or propyl groups are particularly potent even when deficient of a phenolic hydroxyl function[24,25], normally a prerequisite for high activity. Ommission of a 9-methyl group is detrimental

to activity, and this suggests it is an important pharmacodynamic feature of the molecule[77].



(16)

R_1	R_2	isomer	ED_{50}, mg/Kg sc Mice hot plate
Me	Me	α,	3.0
		β,	0.44
Et	Me	α,	1.50
		β,	0.07
Pr	Pr	α,	71.20
		β,	0.8

Morphine = 2.90 ED_{50}, mg/Kg sc

Table 1

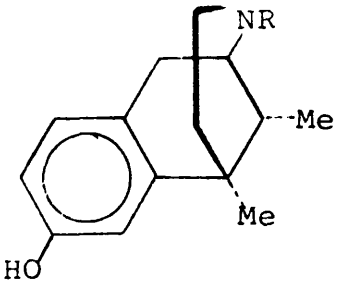
A thorough study of the effect of substitution at the nitrogen in the benzomorphan series was made by Harris and Archer[26]. They, more than any other group, developed and promoted the agonist-antagonist concept of antinociception, which is very prominent in present day analgesic research rationale. Pentazocine (17; $R=CH_2-CH=CMe_2$) is a moderately strong agonist with weak

antagonist activity and is now in clinical use in a wide range of pain situations. Full reviews on its use are available in Goodman and Gilman[3] and Martindale[27]. Cyclazocine (17; R=cyclopropylmethyl) is a powerful morphine antagonist in the D'Amour-Smith assay (7 x nalorphine) with equally powerful pain relieving qualities (0.25mg=10mg morphine), and has proved to be a good research tool. It may yet find application as an analgesic. Phenazocine (17; R=CH_2CH_2Ph; ED_{50}, 0.25 mg/Kg sc, mice) is about 5-10 times more powerful than the parent metazocine (R=Me; ED_{50}, 3.0 mg/Kg sc, mice hot plate) as an analgesic[22].

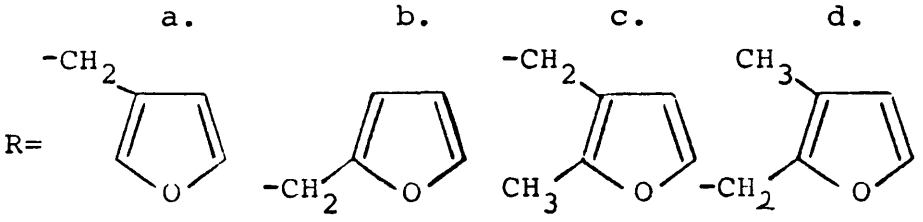
A series of N-furfurylmethyl benzomorphans (17) show interesting pharmacological profiles. The activity profile of (17) may be varied by simple structural changes as shown in Table 2[28]. Compound (17a) is devoid of agonist activity but is an antagonist about equal in potency to nalorphine. Compound (17d) is a pure agonist comparable to morphine, but it did not display straub tail characteristics in mice nor did it substitute for morphine in dependent monkeys[29]. Compounds (17b and 17c) have mixed agonist-antagonist activity.

In contrast to compound (17b), N-2"-tetrahydrofurfuryl-benzomorphans (18a) are devoid of antagonist activity and are potent analgesics[29]. All eight isomers of the derivative (18a) have been studied; 2"S compounds are superior to the 2"R diastereoisomer. Modifications of the N-tetrahydrofurfuryl group markedly affected the action profile and furnished compounds with highly diffe-

rentiated opioid properties[30]. More potent isomers of (18a and 18b) were powerful non-morphine like analgesics with potencies of more than 100 times that of morphine. These potent compounds did not show a positive straub tail test in mice and failed to suppress the abstinence sign in dependent monkeys deprived of morphine, and hence are potential non-addicting analgesics.



(17)

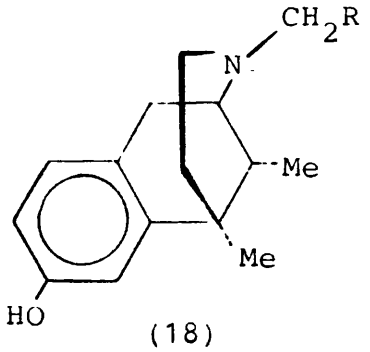


	a.	b.	c.	d.
Antagonist[1]	+++	+++	+	None
Analgesic[2]	None	+	++	+++

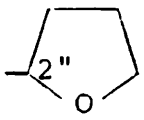
1. 50% suppression of morphine analgesia in mice

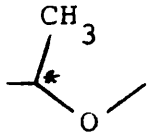
2. Hot plate in mice

Table 2

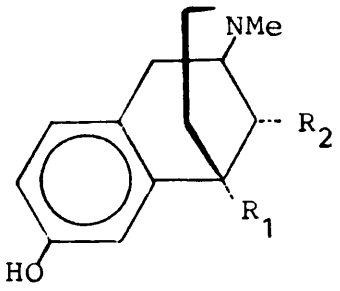


(18)

a) R = 

b) R = 

An interesting aspect of the benzomorphan compounds is the study of the agonist-antagonist profiles of pairs of optical isomers[31] (Table 3). The laevo-isomers are more potent than corresponding racemates and, like racemates, would not support morphine-dependent monkeys. Surprisingly, laevo-isomers, in some cases, showed antagonistic action in precipitating the morphine abstinence signs in these morphine-dependent animals. The laevo-isomers of 5-propyl-9α-methyl-6,7-benzomorphan (Table 3; 19d) is one fifth as potent as nalorphine as an antagonist but stronger than morphine as an analgesic. Some dextro-isomers are also active and, surprisingly shows some capacity to substitute for morphine. However this phenomenon of separation of morphine-like effects in enantiomers is not general for this series[32]. For instance both isomers of 5-methyl-9α-ethyl-6,7-benzomorphan (Table 3; 19c) are active and neither shows the capacity to substitute for morphine, nor do they manifest any antagonist effect.



(19)

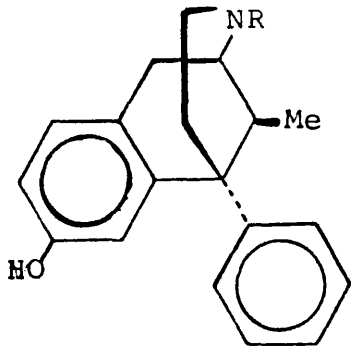
	R_1	R_2	Enantiomer	ED_{50}, mg/Kg	PDC	Antagonist Potency
a.	Me	Me	(-)	0.6	No	1/50-1/10 nalorphine
			(+)	Inactive	No	No
b.	Et	Et	(-)	1.2	No	1/10 nalorphine
			(+)	7.5	Inter-mediate	No
c.	Me	Et	(-)	0.7	No	No
			(+)	11.7	No	No
d.	Pr	Me	(-)	0.8	No	1/5 nalorphine
			(+)	12.3	High	No
	Morphine			1.2	High	No

Table 3 Analgesic activity, physical dependence capacity (PDC) and antagonistic potency of some benzomorphan enantiomers.

The synthesis, analgesic activity and physical dependence capacity of a large number of 5-phenyl benzomorphan derivatives has been reported by Clark et al [33,34]. Such compounds provide a structural link between the benzomorphans and the 4-phenylpiperidines and diphenylpropylamine analgesics. The 9-methyl-5-phenyl derivative (20; R=Me) was obtained by an adaptation of the Grewe-type synthesis. Only one diastereoisomer resulted and, unexpectedly, this had a β-configuration[33]. The laevo-isomer of 20 (R=Me) is twice as potent as morphine as an analgesic, with nalorphine-like properties in precipitating the morphine abstinence in non-withdrawn, dependent monkeys. The laevo-isomers of the N-dimethyl-allyl- and N-cyclobutylmethyl analogues of 20 are both mixed agonist-antagonists but are less potent than the corresponding 5,9-dialkyl-6,7-benzomorphan derivatives either as analgesics or as antagonists. The N-propargyl analogue ((-), 20;R=$CH_2C{\equiv}CH$) is a pure, long acting antagonist in the guinea pig ileum[34].

Most of dextro-isomers (20) with antagonist-like substituents are inactive or very weak as analgesics.

May et al[32,35,79,82] prepared 2-methyl-6,7-benzomorphan and 2,9-dimethyl-6,7-benzomorphan to acertain the importance of the quaternary carbon in rigid structures. Compounds (Table 5) with H at position 5, although somewhat reduced in potency from corresponding 5-methyl relatives, are nevertheless moderately to strongly active. All the nonquaternary-carbon compounds



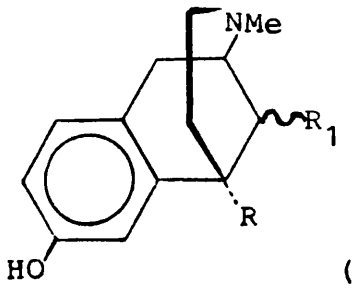
(20)

R	isomer	ED_{50}, mg/Kg sc
Me	(-)	0.18
Me	(+)	3.40
CH_2CH_2Ph	(±)	Inactive
Metazocine	(±)	0.44

Mice hot plate test.

Table 4

as racemates show mixed agonist-antagonist action in the morphine-dependent monkey, similar to laevo-isomers in the 5-alkyl series. Recently the improved synthesis of 9α- and 9β-methyl compounds (16c and 16f) has been reported by Gless and Rapport[36]. Surprisingly, a secondary amine analogue of (16b; $R=R_1=H$) without quaternary carbon is codeine-like in analgetic activity (ED_{50}, 10.2 mg/Kg sc) as determined by the mouse hot plate test[104].



(16)

		ED_{50}, mg/Kg sc
a.	R=Me, R_1=H	3.2
b.	R=R_1=H	4.5
c.	R=Me, R_1=9α-Me	1.2
d.	R=H, R_1=9α-Me	4,3
e.	R=CH_3, R_1=9β-Me	O.1
f.	R=H, R_1=9β-Me	1.1
	Morphine	2.1

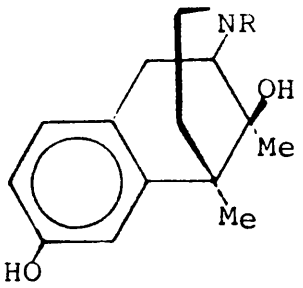
Determined hot plate method, in mice.

Table 5

The effect of introduction of a 9-hydroxyl group (equivalent to the 14-hydroxyl of the morphine analogues) has been examined in the benzomorphan series[96]. A 9-hydroxy substituent reduces the analgesic activity of metazocine (21; R=Me), the influence of the β-positioned group being more deterimental[17]. Introduction of an 9β-hydroxy group onto the benzomorphan bearing an allyl or cyclopropylmethyl group on nitrogen (21; R=CH_2-CH=CH_2, or R=CPM) increased antagonist activity but

decreased agonist activity. In the case of cyclazocine, a 9β-hydroxyl group raised the antagonist activity by ten fold, while agonist activity decreased by about 400 fold. On the other hand, introduction of an 9α-hydroxyl group had no influence on the antagonist action of pentazocine or cyclazocine[37].

Some potent analgesics with agonist-antagonist profiles have been derived from 5-allyl-9β-hydroxybenzomorphan (22). The N-cyclopropylmethyl and N-cyclobutylmethyl derivatives of 22 were effective agonists in the mice writhing text, both effectively antagonised the action of oxymorphone. In both respects, the N-cyclopropylmethyl compound was more potent[38]. An 9α-methyl group abolished the analgesic properties of the N-cyclopropylmethyl derivative of 22 but enhanced its antagonist action, whereas it increased the potency of the N-cyclobutylmethyl derivative of 22 both as an agonist and antagonist.



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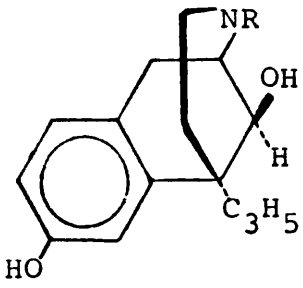

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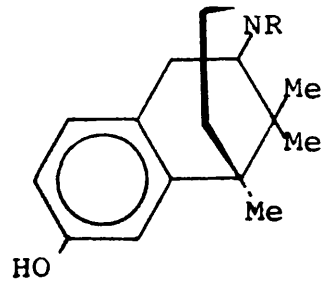
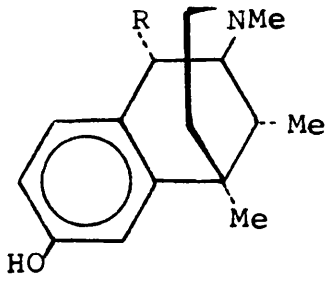


(23)

a. R=CPM b. R=CBM

Introduction of another methyl group at C-9 in certain 5,9-dimethylbenzomorphan derivatives, as in (23), gave a series of compounds which possessed pharmacological profiles similar to the 9-monomethyl series, but they were generally more potent and longer acting[39].



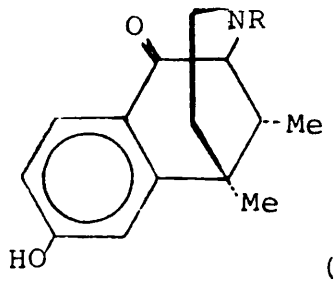
(24)

R	ED_{50}, mg/Kg sc
a. R=Ph	2.5
b. R=Me	0.6
pentazocine	20.4

Mice, tail flick antagonist of morphine

Table 6

The structure-activity effects of altering the substituents at other positions on the ring system have been studied. Ziering et al[85] introduced methyl groups into the 8α- and 3'-positions, and phenyl into the 8α-position of the benzomorphan nucleus. The 8α-phenyl- and 8α-methylbenzomorphan derivatives (Table 6; 24a & b) are surprisingly active as antagonists for N-methylated-6,7-benzomorphan.



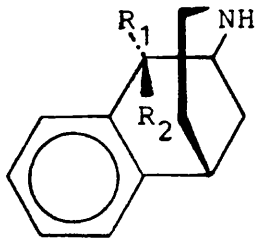
(25)

	AD_{50}, mg/Kg sc Antagonist	ED_{50}, mg/Kg sc Agonist
R=CPM	7.2	0.16
cyclazocine	0.02	0.15
pentazocine	3.9	2.2

Table 7

Direct introduction of oxygen in the benzylic carbon provided another subseries with mixed agonist-antagonist properties[105] (Table 7). Introduction of an 8-keto group in certain benzomorphan antagonists invariably reduced antagonist activity without appreciably effecting agonist

activity. However, antagonist activity increases when such a change is made in norbase (25; R=H). The 8-oxo analogue (25; R=CPM) of cyclazocine possessed agonist activity similar to cyclazocine, and an antagonist activity similar to pentazocine. A few 8-hydroxy-6,7-benzomorphans[104,105] have been reported, all of low potency either as agonists or antagonists. For example, the diastereomerically related 8α- and 8β-hydroxy-6,7-benzomorphans (Table 8, 26) are weak analgesics. The 8β-hydroxy isomer was more potent than the α-isomer. Surprisingly the N-methyl derivative of 26 was inactive. This is unexpected on the basis of the classical structure action-relationships of analgesic 6,7-benzomorphans. The tertiary amine would be expected to be a more potent analgesic than the secondary amine[104].



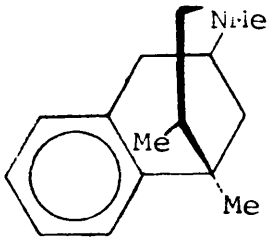
(26)

R_1	R_2	isomer	ED_{50}, mg/Kg sc
OH	H	α	56.5
H	OH	β	13.7
2-methyl-8β-hydroxy-6,7-benzomorphan			Inactive

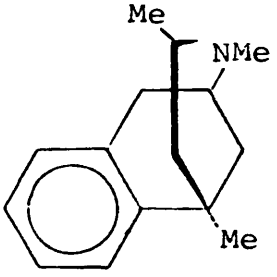
Mice hot plate

Table 8

A series of 3,5-dimethyl- and 4,5-dimethylbenzomorphan derivatives were prepared by Parfitt and Walters[40]. The non-phenolic 4,5-dimethyl-6,7-benzomorphan (27) showed significant analgesic activity and was more active than 3,5-(28) or 5,9-positional isomers (mice hot plate). The N-cyclopropylmethyl derivative of 28 was about half as potent as morphine and the most active compound of the series. Surprisingly, the N-cyclopropylmethyl analogue of the more active 27 proved to be inactive. The N-phenethyl derivatives of 27 and 28 were without activity.



(27)

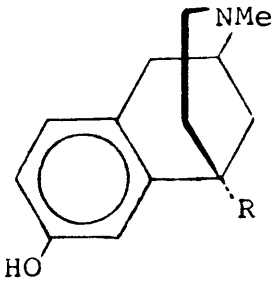


(28)

ED_{50}, 4.2 mg/Kg sc ED_{50}, 11.9 mg/Kg sc

(Mice hot plate)

As a hybrid of both the benzomorphan and piperidine analgesics May prepared 2-methyl-5-carboethoxybenzomorphan (29a)[41]. The analgesic activity of 29a is comparable to meperidine, and it did not support morphine dependence in monkeys. The benzomorphan-prodine hybrid (29b)[42] is about one quarter as active as morphine, and does support morphine dependence in monkeys.



(29)

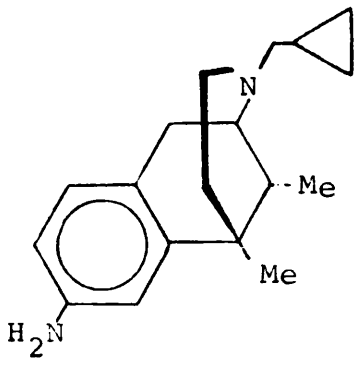
R	ED_{50}, mg/Kg sc
a. $COOC_2H_5$	10.1
b. OCOMe	5.1

Mice hot plate.

Table 9

It was anticipated that replacement of the 2'-hydroxyl group in benzomorphans by an amino group would give an analgesic less subject to metabolic inactivation, and thus render it longer acting. The 2'-amino analogue (30) of non-phenolic cyclazocine was found to be a strong, active analgesic agonist with antagonist properties and had a favorable oral/parenteral ratio[43,44].

Michne et al [45] have reported the synthesis and analgesic activity of a large number of 9-propanol-6,7-benzomorphans (31). The structure-activity profile of 31 analogues differs from the structurally similar bridged oripavine derivatives. In general, these variants had weak analgesic properties but were potent antagonists. The N-methyl derivative of 31 (R_1=R_2=Me, R_3=$(CH_2)_2CH$(-



(30)

	ED_{50}, mg/Kg sc[a)]	AD_{50}, mg/Kg sc[b)]
(30)	0.8	2.7
Cyclazocine	0.15	0.028

a) acetylcholine writhing test.

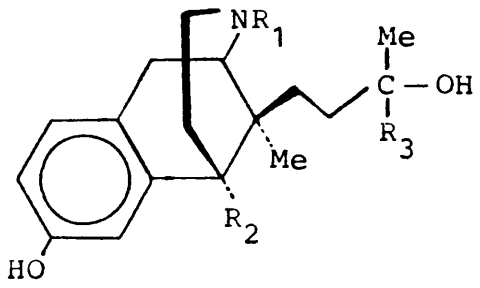
b) pentazocine antagonism.

Table 10

$CH_3)_2$) is five times as potent as nalorphine and represents the most potent N-methyl antagonist reported to date[46]. A series of 9-(3-oxoalkyl)-6,7-benzomorphans (32)[47], where the alkyl group was a straight chain or terminally branched chains containing from one to six carbon atoms, were synthesized. Several compounds (32; R=C_3H_7, C_4H_9, $CH_2CH(CH_3)_2$, $(CH_2)_2CH(CH_3)_2$) displayed activity up to 100 times that of morphine. Compound 32 containing five or six carbon atoms in the alkyl chain exhibited antagonist activity.

Various skeletal modification of the benzomorphan ring have been reported. These include C-ring expansion to form the homobenzomorphan, introduction of a second

nitrogen, contraction of B or C ring and synthesis of the basic skeleton with nitrogen in different positions. A notable example are homobenzomorphans of type (33), prepared by variant of the tetralone route[48]. These compounds have significant agonist and antagonist activity depending upon the nature of the N-substituent. The β-isomers with an antagonist N-substituent (33; R=CPM or $CH_2CH=C(CH_3)_2$) may be classified as 'pure' antagonist while the corresponding α-isomers also display agonist properties.



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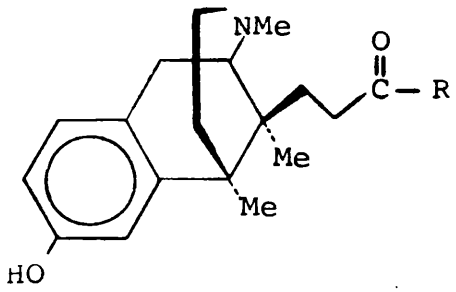

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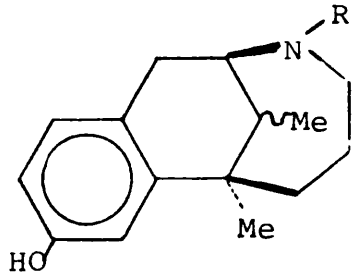


(33)

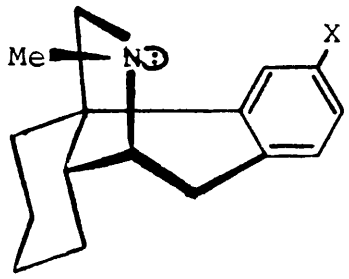
1.3 Opiate receptors.

There are several structural features common to narcotic analgesic drugs[55]. Many strong analgesics contain an aromatic ring bonded to a saturated two- or three-carbon chains terminating with an amine nitrogen. Other additional features are associated with strong analgesic activity[49,50]. In morphine analogues, the presence of a phenolic hydroxyl, tertiary nitrogen, and quaternary benzylic carbon all enhance analgesic activity.

It is generally agreed that an essential feature of an analgesic drug is its basic nitrogen, which either forms part of an alicyclic ring structure or an acyclic chain. In most examples, the base is tertiary, but there are number of secondary amines[51,52] with analgesic properties. The low analgesic potencies of nor-analogues is considered to be due to distribution factors and not to the failure of such derivatives to associate at the receptors[53].

The cationic (protonated) form of the drug is generally accepted to be the active species and to interact with the receptor *via* ionic association[53-55]. Belleau *et al*[56], however, recently proposed that the nitrogen lone pair orientation is a key factor governing association of an opiate drug with its receptor, and ruled out the protonated form as the active species[56]. This was postulated after comparision of the X-ray structure of *N*-methyl-D-[nor]morphinan salt (34), which is

devoid of analgesic or antagonist activity, with that of the morphinan salt (35). Belleau et al pointed that the protonated nitrogen lone-electron pair of the D-nor-morphinan (34) is directed towards the aromatic feature of the molecule, whereas the same feature points away from aryl in morphinan or benzomorphan salts. An objection to these views is the fact that morphine metho-salts (in which the lone-pair is not available and nitrogen atom carries a full positive charge) are similar in potency to morphine itself when administered directly into the brain[37].



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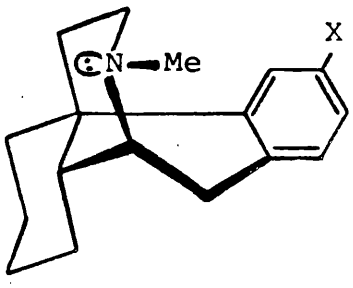


(35)

Opiate receptors are stereoselective towards a variety of narcotic analgesics and in all cases activity is distributed unevenly in enantiomeric forms. Beckett and Casy[53], in 1954, formulated a receptor model on the basis of stereochemical evidence and structural features common to analgesics and their antagonists known at that time. It was postulated that the receptor possessed a flat surface, a cavity and an anionic site which were thought to accommodate an aromatic ring,

hydrocarbon moiety and a protonated basic nitrogen respectively (Figure 1).

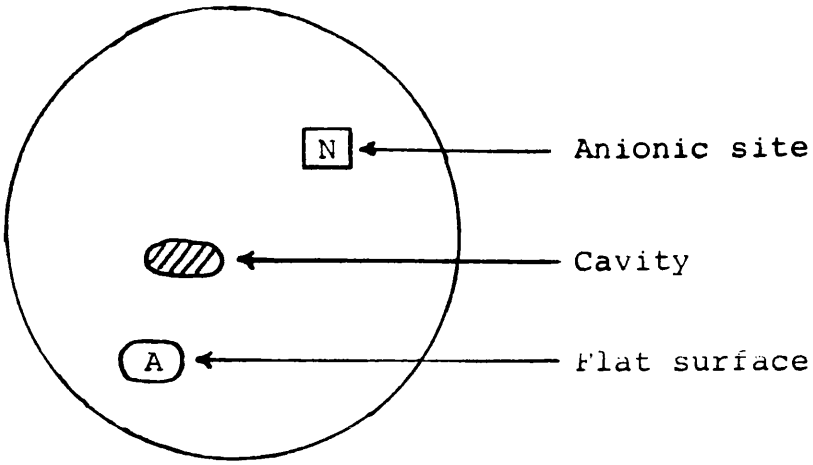


Figure 1

A number of proposals that update Beckett's receptor model have been made in the light of new information. Bentley and Lewis[12] proposed an extension of the receptor (Figure 2) to include a lipophilic site which would accommodate the very potent 6,14-endoethenotetrahydro-thebaine and oripavine series. An alternative proposal, attempting to account for stereochemical anomalies among certain compounds where both members of an enantiomeric pair show significant pharmacological activity, for example 5-phenyl-6,7-benzomorphan (19), has been advanced by Galt[58]. He proposed an extension of the planar binding area (A), as shown in Figure 3. Any molecule, according to Galt, which has, or can project, a planar surface and cationic centre in the same juxtaposition in space as the model, could have opiate properties. Thus, both enantiomeric forms of 5-phenyl-6,7-benzomorphan provides features required to fit the model; the nitrogen

atom and phenolic hydroxyl superimpose, but the aromatic rings do not overlap.

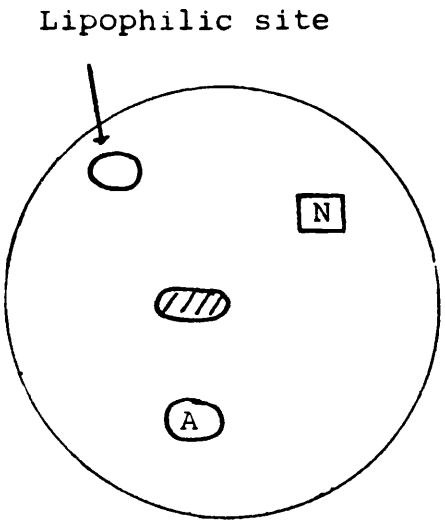


Figure 2

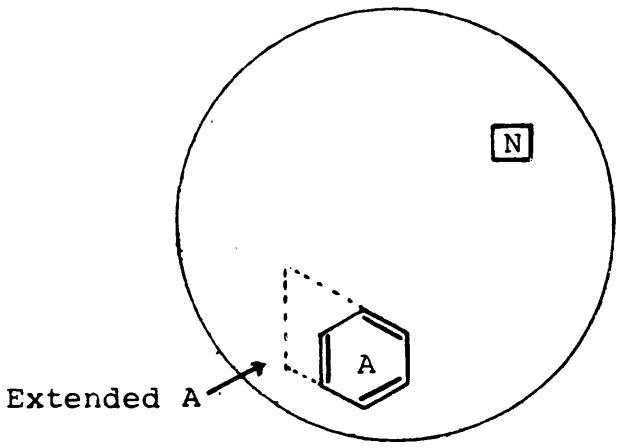


Figure 3

Snyder et al[55] proposed a model attempting to explain the structure-activity relationships of opiate agonists and antagonists, and the importance of sodium. They suggest the receptor exists in two conformations allosterically modulated by sodium ions, the agonist and antagonist (Figure 4). Two sites, one of lipophilic and one of anionic character that interact with the aromatic ring and amine nitrogen respectively, are available in both conformations. In addition, the receptor has a specific agonist site (F), which is not available to the antagonist molecule, and binding of agonists to this site stabilizes the agonist conformation. Antagonist also have a specific binding site capable of interaction with antagonist substituents and its occupancy stabilizes the antagonist conformation. Normally, the receptor is in the antagonist conformation because of the prevailing brain sodium ion concentration.

The enhanced potency of econitasene, phenazocine, fentanyl and the bridged thebaines is attributed to the fact that such molecules have aromatic features capable of binding to both A and F sites. Mixed agonist-antagonists are considered to interact with both agonist and antagonist conformations. The failure to design narcotic antagonists based on phenylmorphans by linking the basic centre to groups such as allyl and cyclopropylmethyl is suggested to be due to the aromatic rings of such compounds interacting with specific agonist site F rather than A site.

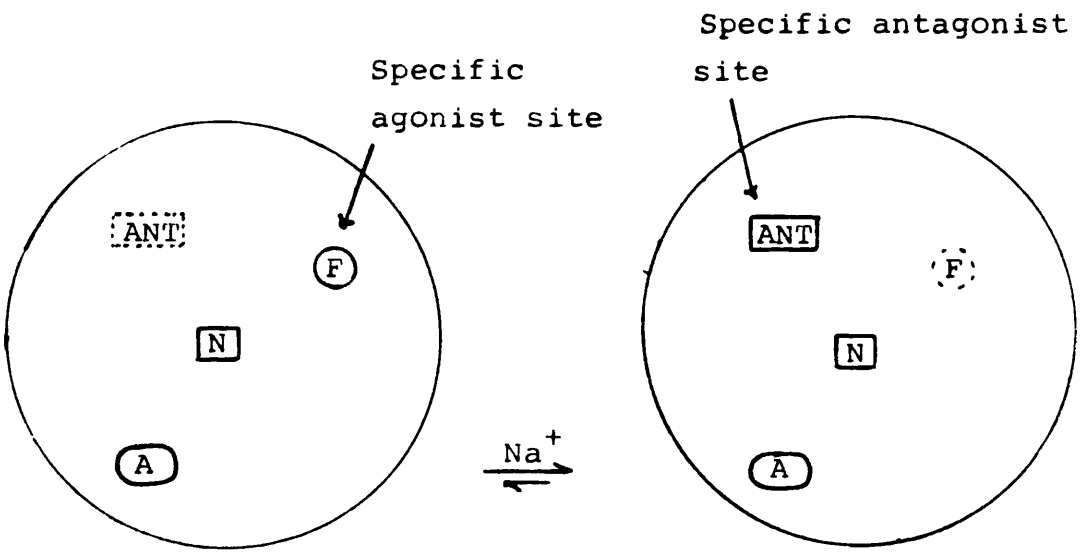


Figure 4

In this model agonist and antagonist activities are associated with axial and equatorial N-substituents respectively and the effect of the C_{14}-OH group in enhancing antagonist activity is explained by assuming its presence is responsible for a shift from axial to equatorial N-substituent. Quantum chemical studies carried out by Loew *et al*[59] do not support this

hypothesis. They found no correlation between agonist-antagonist potency variation and calculated axial-equatorial N-substituent characteristics. Loew et al suggest that agonist-antagonist activity is regulated by two different low energy equatorial N-substituent conformers, and the C_{14}-OH and N-substituent interact indirectly through a common anionic site[60]. Alternatively, Casy proposed that the hydroxyl group may exert its influence electronically by inducing an electron drift towards the $RN^{+}H$ feature via an $N^{+}H$--OH hydrogen bonding mechanism[61].

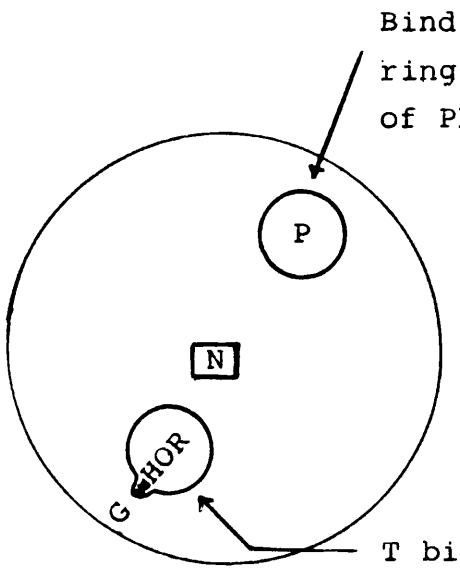
A variant of the Snyder model in which only one conformation of the receptor is needed for both agonist and antagonist molecules was proposed by Vera Kolb[62]. There are two different spacially fixed amine binding sites: one agonist and one antagonist. The opiate undergoes binding to its amine binding site via the lone-pair electrons on nitrogen. It is suggested that the primary action of antagonists at the receptor is through the interaction of the antagonist N-lone pair and its amine-site, and not through some lipophilic association of the N-allyl chain with a specific antagonist binding site. The main role of the N-allyl chain is to force the N-lone pair lobe of an antagonist molecule in the direction of its amine binding site[63].

Each of the proposed models can account for some of the experimental observations but none is satisfactory. The concept of a single receptor at which all

ligands associate by mechanisms that are essentially alike, appears improbable. Binding interactions of so restricted a character are incompatible with present stereochemical and structure-activity data.

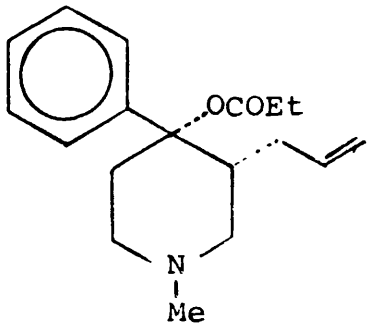
Portoghese, in 1965, introduced a new concept on the mode of interaction of ligands with opiate receptors[64]. He proposed multiple modes of interaction which arise from association of different ligands with different recognition loci on either a single or a group of related receptors. A method of determining similarities or differences in molecular binding modes by comparing the variation of activity in different series of compounds when identical changes in the N-substituent are made, was proposed. Comparision of meperidine derivatives with identically substituted benzomorphans showed no parallel relationship[64], and thus implies dissimilar modes of binding.

The loss of activity upon introduction of a meta phenolic OH in allylprodine (36), which is in marked contrast to the enhancement of agonist potency conferred by this group in morphine, is attributed to divergent binding modes. Portoghese et al postulated that this difference arises from the recognition of the aromatic groups of morphine and allylprodine by different aromatic-binding subsites of the receptor. These subsites are suggested to be identical with those which recognize the aromatic rings of the Tyr^1 and Phe^4 of the enkephalins and endorphin (Figure 5)[65].



Binding site of aromatic ring of allylprodine and of Phe^4 enkephalin

T binding site of aromatic rings of morphine and of Tyr^1 enkephalin



(36)

Figure 5

Evidence of competitive kinetics and the fact that antagonist molecules like nalorphine block a wide range of analgesics support the view of a single receptor species. However, the differential pharmacological responses seen with various opiates, and the differential competitive displacement of various opiates by narcotic agents from the receptor suggests that there are multiple receptors[66,67].

Martin et al postulated the existence in the brain of μ, κ and σ receptors on the basis of the different pharmacological responses observed with a variety of narcotic analgesics in the non-dependent chronic spinal dog. Morphine is the prototype agonist of the μ receptor, Ketocyclazocine for the κ, and SKF-10047 (N-allyl analogue of normetazocine) for the σ receptor[66]. The effects of these drugs are antagonized by naltrexone, indicating

that they are agonists. Pentazocine is suggested to be a weak μ receptor antagonist and a moderate κ and σ agonist. The antagonistic action of pentazocine at the μ receptor is the reason why pentazocine precipitates abstinence in persons dependent on morphine. Its agonistic action at the κ receptor accounts for its analgesic activity and for the induction of the nalorphine-type of physical dependence. Agonistic effects at σ receptors accounts for the psychotomimetic effects. Cyclazocine is suggested to have both κ and σ agonistic activity but no activity at the μ receptor.

The Martin et al hypothesis has been confirmed biochemically by demonstrating the presence in brain[68] as well in isolated organs[69] of at least two kinds of sites for radio-labelled analogues of enkephalins. These compounds bind to a low affinity site where they are readily displaced by natural and synthetic opiates, and to a high affinity site which exhibits a high preference for the peptide structure. From a comparision of the binding properties and the pharmacological potency on isolated organs, the low affinity site has been related to the μ receptors (or morphine receptors) of the guineau pig ileum and the high affinity site has been related to σ receptor (or enkephalin receptors) of the mouse vas deferens[68,69]. Several biochemical differences between the binding sites exist. Sodium selectively inhibits opiate agonist binding by abolishing high affinity, with minimum effects on the low affinity site[70]. Structure-activity studies with selective

enkephalin analogues have provided support for the hypothesis that analgesia is mediated by the μ receptor. The σ receptors are considered to be involved with behavioral effects[71].

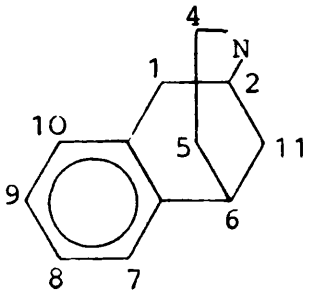
The actual structure and mechanism of action of opiate receptors must await the isolation of receptor material in a pure and viable state. Numerous attempts to obtain an active solubilised receptor have so far met with very limited success. Recently successful solubilization of receptor in a state that reversibly binds opiate ligands, using new types of detergent, has been reported[72]; hopefully this will lead to further progress.

The concept of the analgesic receptor has been progressively modified with new experimental information. Casy, in 1978, concluded that the Portoghese hypothesis of multiple modes of ligand-receptor interaction, whether at a single receptor or a variety of linked receptor sites, was a reasonable one in the light of present day stereochemical and other structure-activity data[61].

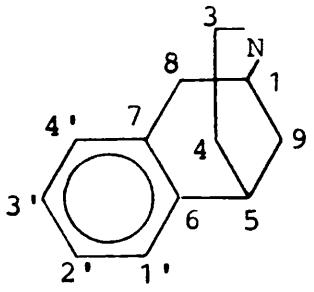
1.4 Chemistry of benzomorphanones

1.4.1 Nomenclature

There are two systems of nomenclature used for the benzomorphans. The Chemical Abstracts name for the parent ring system is 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (37), but is better known as 6,7-benzomorphan (38) which is the original nomenclature. The numbering system differs as shown.



(37)



(38)

1.4.2 Synthetic routes to benzomorphanones.

The principal synthetic routes for constructing the ring system are shown schematically only (Figures 8-16). The Grewe and tetralone routes, as well as modification of these methods, are by far the most important synthetic routes.

The first compound containing the benzomorphan nucleus was prepared by Baltrop[73] in 1947. He synthesized the ethobromide salt of 2-ethyl-5-methyl-9-oxobenzomorphan from the β-tetralone (39). May and Murphy[74] prepared

2,5-dimethyl-6,7-benzomorphan (40) exploiting this route (Figure 6) and by a longer synthesis starting with hydratroponitrile (Figure 7). The β-tetralone route has been widely used[75-77] in the preparation of various 5-alkyl benzomorphans and also in the preparation of homobenzomorphan (33).

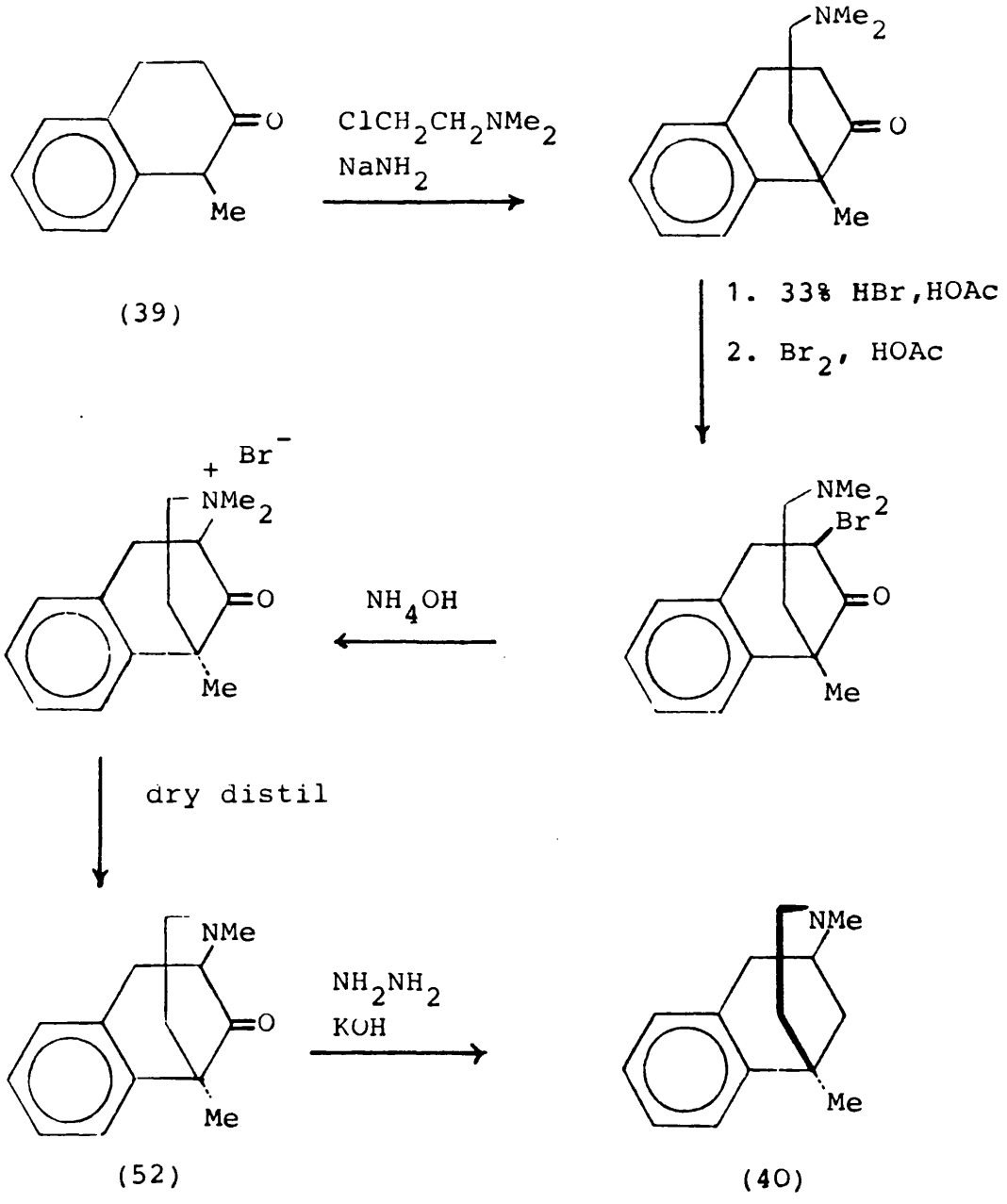


Figure 6

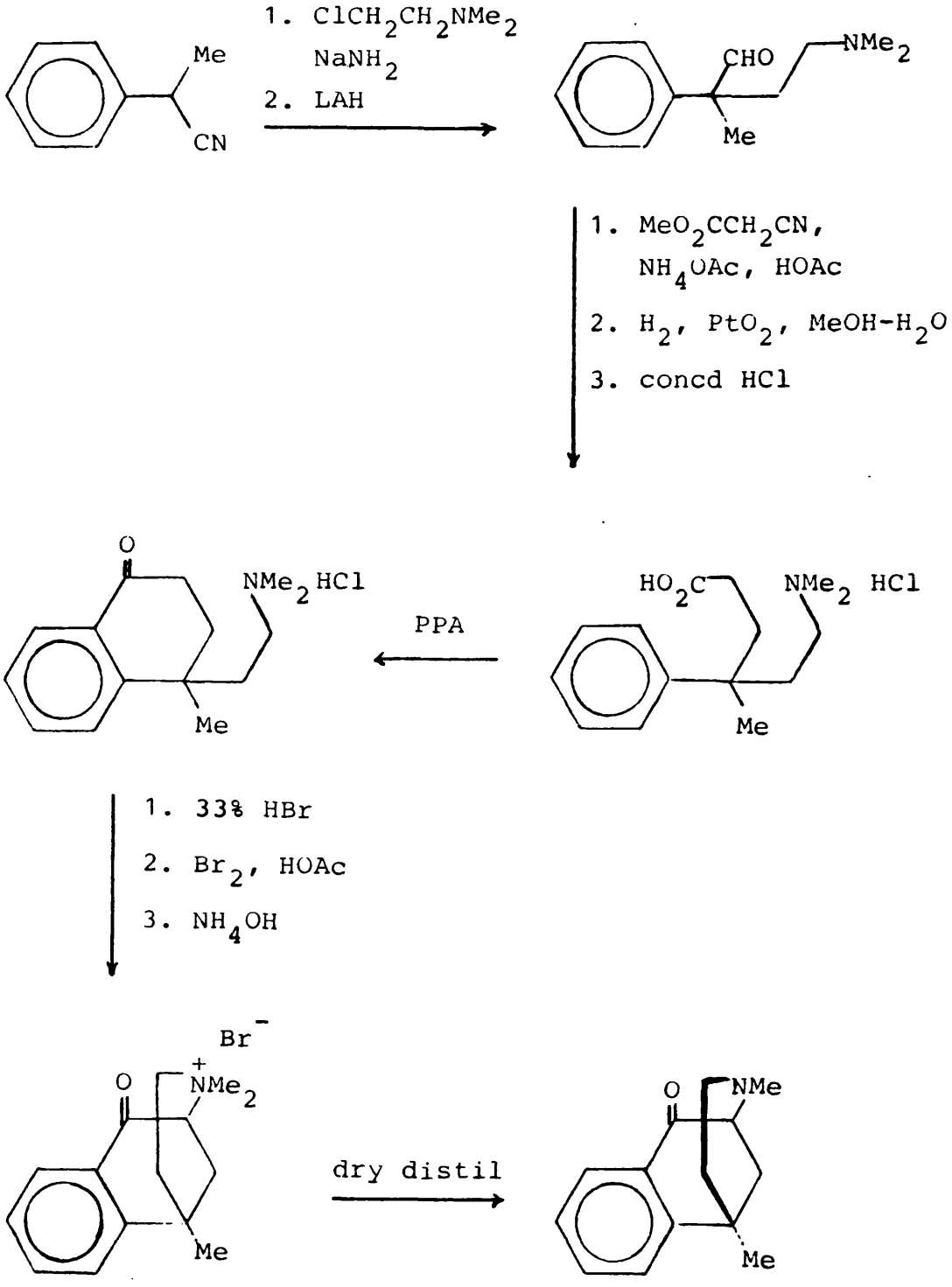

1. ClCH2CH2NMe2
NaNH2
2. LAH
Me
CN
CHO
NMe2
Me
1. MeO2CCH2CN,
NH4OAc, HOAc
2. H2, PtO2, MeOH-H2O
3. concd HCl
O
NMe2 HCl
Me
PPA
HO2C
NMe2 HCl
Me
1. 33% HBr
2. Br2, HOAc
3. NH4OH
Br−
+
O
NMe2
Me
dry distil
O
NMe
Me

Figure 7

Mitsuhasi et al [78] employed the tetralone route to prepare the nonquaternary carbon compound, 2-methylbenzomorphan (Figure 8; 42) which was previously prepared by Kanematsu, Parfitt et al by an alternative route[79] (Figure 9). Mitsuhasi's approach to the preparation of the tetralone precursor (41) involved a Beckmann rearrangement of 4-phenylcyclohexanone oxime followed by hydrolysis, N-methylation, and cyclization. This was converted in the usual manner into to 2-methylbenzomorphan (42).

Kanematsu, Parfitt et al prepared 2-methylbenzomorphan (Figure 9; 42) starting from 4-phenylpyridine[79].

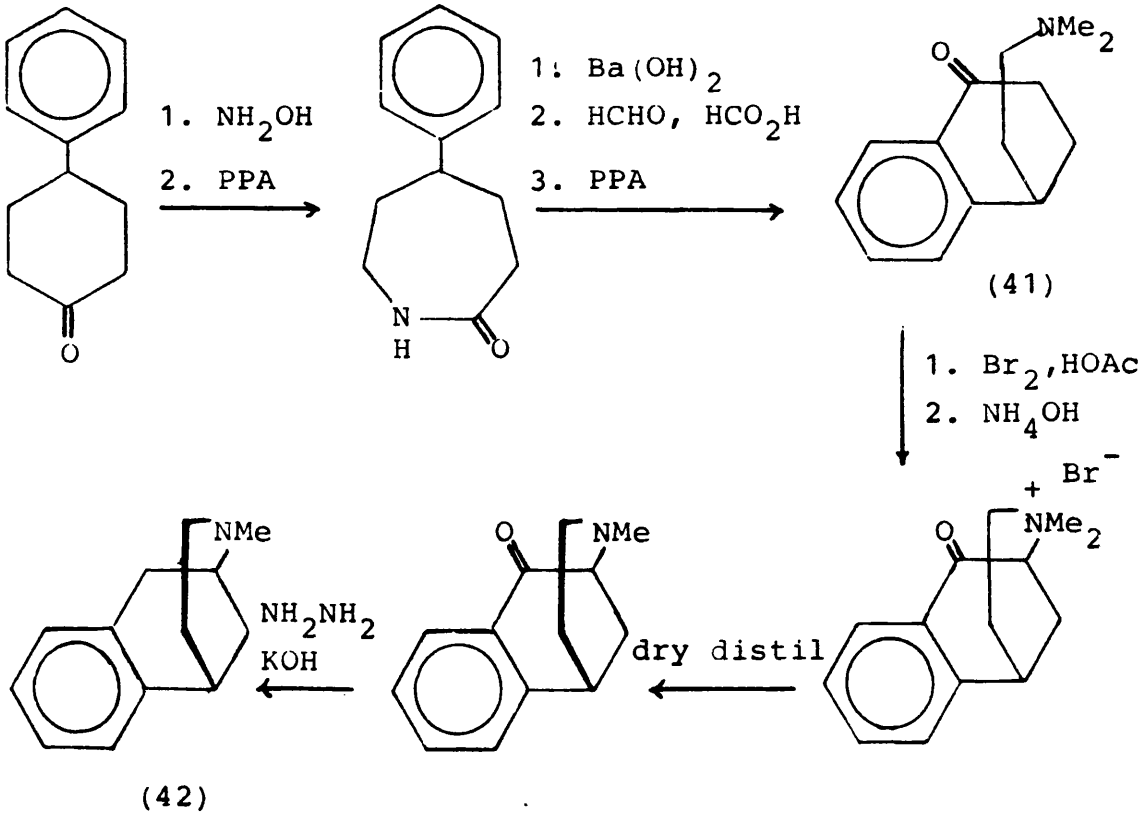
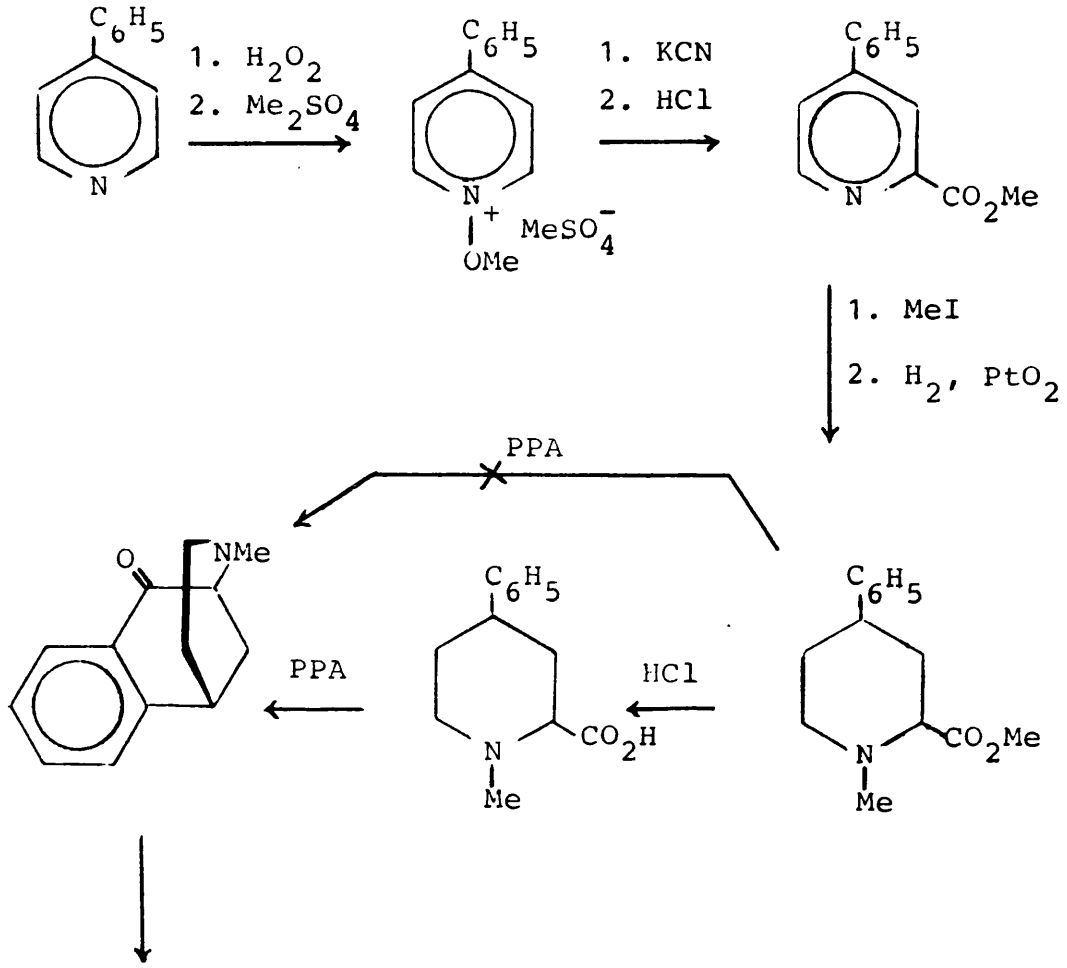


Figure 8



(42)

Figure 9

The preparation of 5-phenyl-6,7-benzomorphan[80] involved the base catalyzed cyclization of the amido tetralone (43), which was prepared by alkylation of benzene with γ-carboethoxy-γ-phenylbutyrolactone (Figure 10).

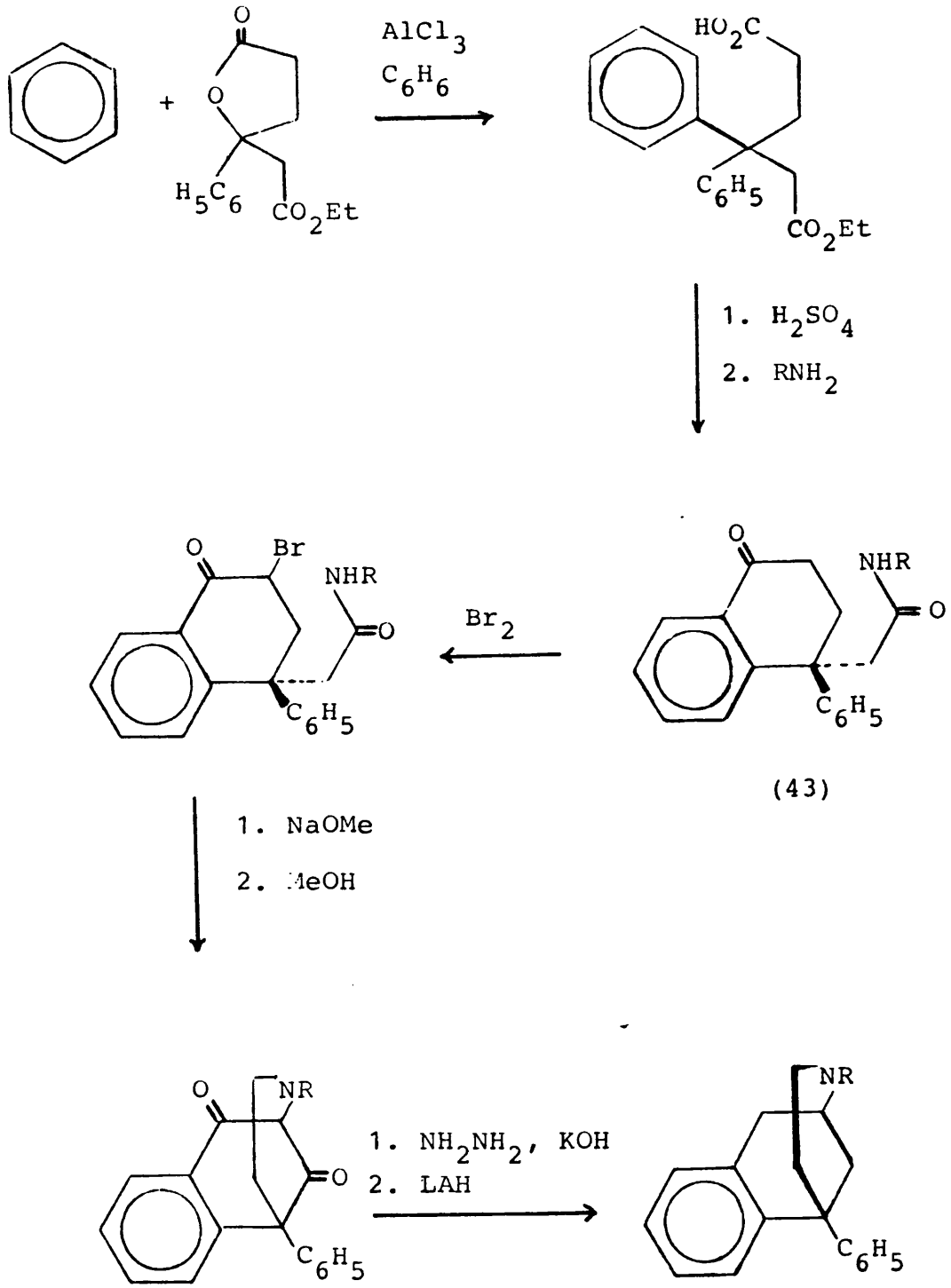

AlCl3
C6H6
HO2C
C6H5
CO2Et
1. H2SO4
2. RNH2
Br2
NHR
(43)
1. NaOMe
2. MeOH
1. NH2NH2, KOH
2. LAH
R = H or Me

Figure 10

The preparation of 2,9β-dimethyl-6,7-benzomorphan (Figure 11; 46), unattainable by the usual Grewe cyclization, has been achieved utilizing the tetralone method[81].

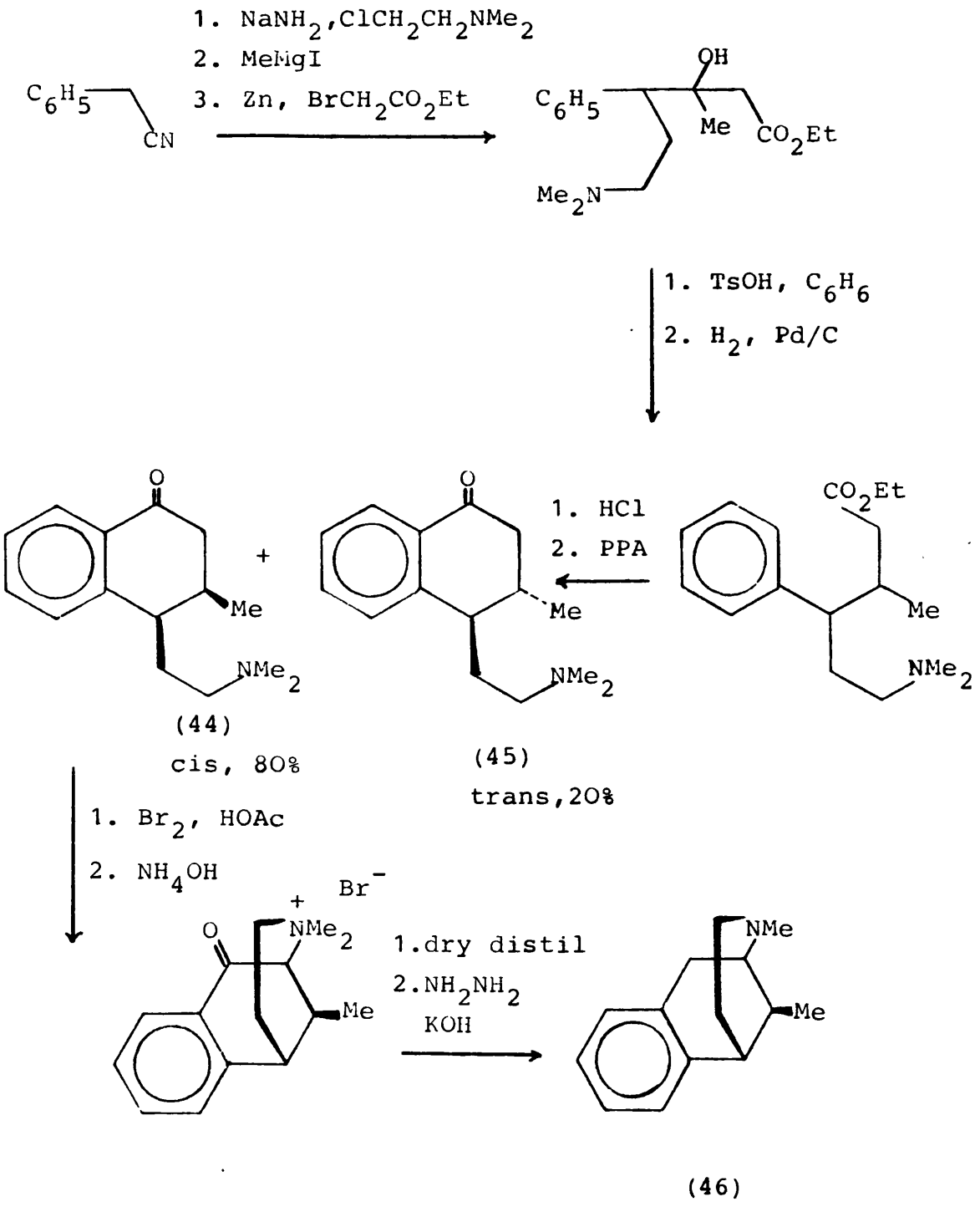


Figure 11

A modification of this synthesis, in which cyclization is effected by mercuric acetate oxidation[82], has been used to prepare the 9α-methylbenzomorphan (Figure 12; 50) from the corresponding trans-α-tetralone (47). The formation of the 2,9β-dimethyl derivative (49) was postulated to arise from inversion (by allylic rearrangement) at C-2 of the key intermediate (48).

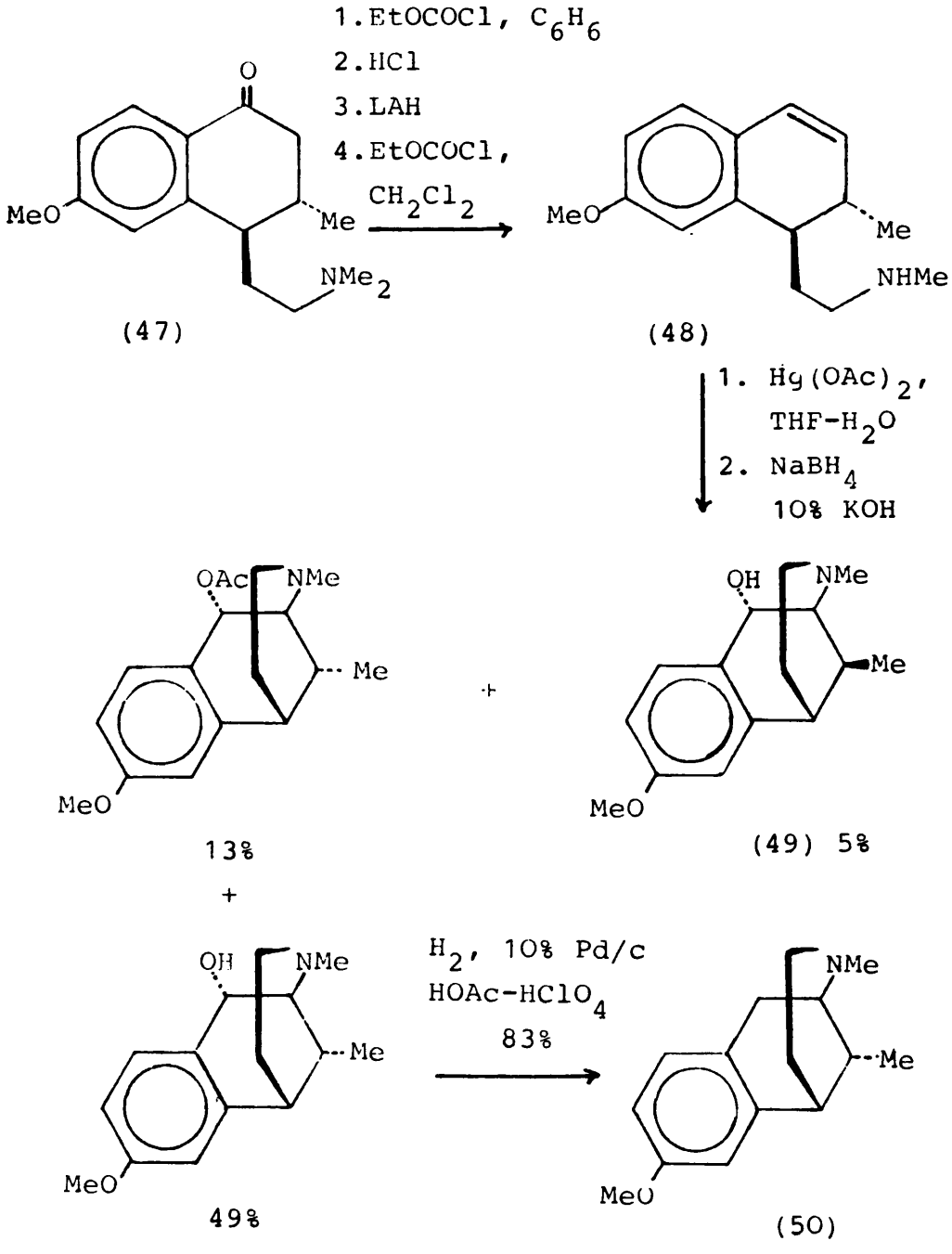
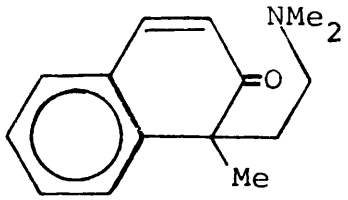


Figure 12

The β-tetralone syntheses referred to above all suffer from low overall yield, and there are problems associated with cyclisation and demethobromination steps due to the formation of elimination products of the type 51.



(51)

A novel synthesis to overcome these problems involves bromination and rearrangement of heterocyclic enamines[83] (Figure 13; 52). For example, Gerry Kavadias et al[84] synthezised 9-oxobenzomorphan with various substituents at the 2,2' and 5 positions in good yields by a modification of this process.

8-Oxo-6,7-benzomorphan has been prepared by oxidation of previously prepared benzomorphans with chromic acid[85,93,104]. The most widely used approach to benzomorphan synthesis is based on the Grewe cyclization of tetrahydropyridines [88-95] (Figure 23, page 64). This method is analogous to Grewe's synthesis of morphine.[86].

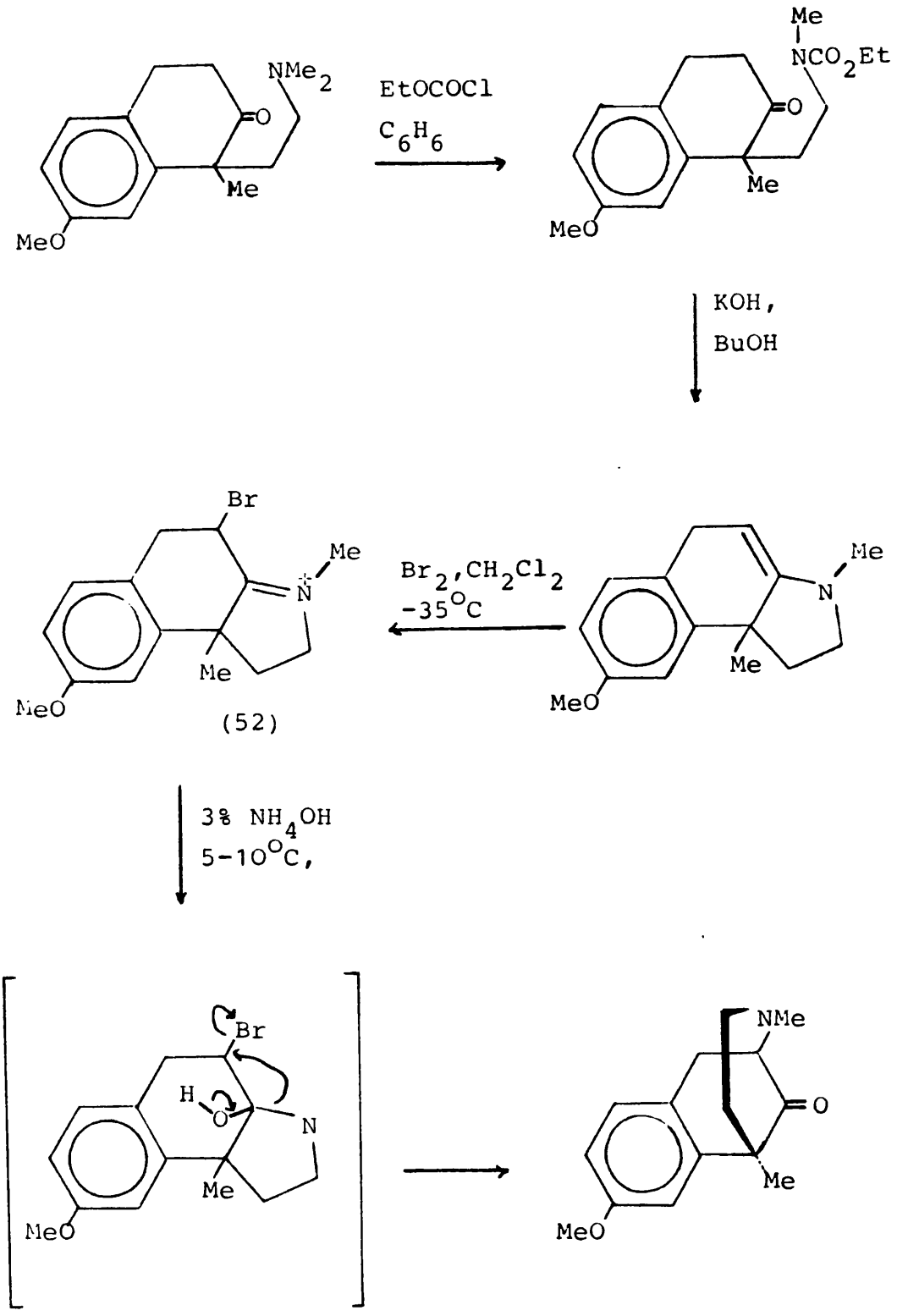

NMe2
EtOCOCl
C6H6
Me
NCO2Et
MeO
KOH,
BuOH
Br
Br2,CH2Cl2
-35°C
(52)
3% NH4OH
5-10°C,
H
O
N

Figure 13

1 .4.3 Reactions of benzomorphanones.

Benzomorphanones provide useful intermediates which have been used for the synthesis of a variety of benzomorphan derivatives. Reduction of 9-oxobenzomorphan (52) with platinum oxide[96,97] or sodium borohydride[98] yielded 9α-hydroxybenzomorphan (53), whereas similar reduction of its methobromide gave, after thermal

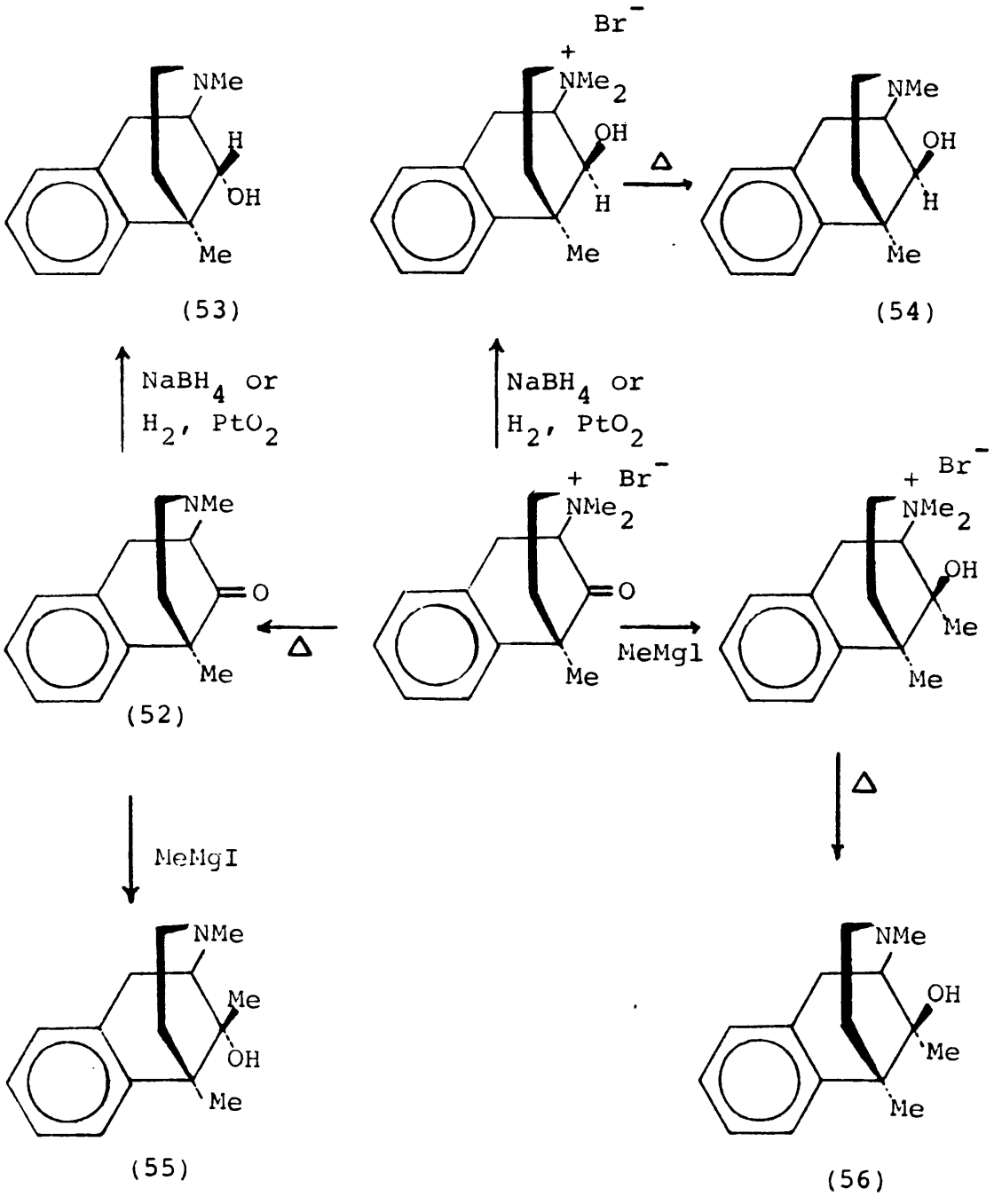
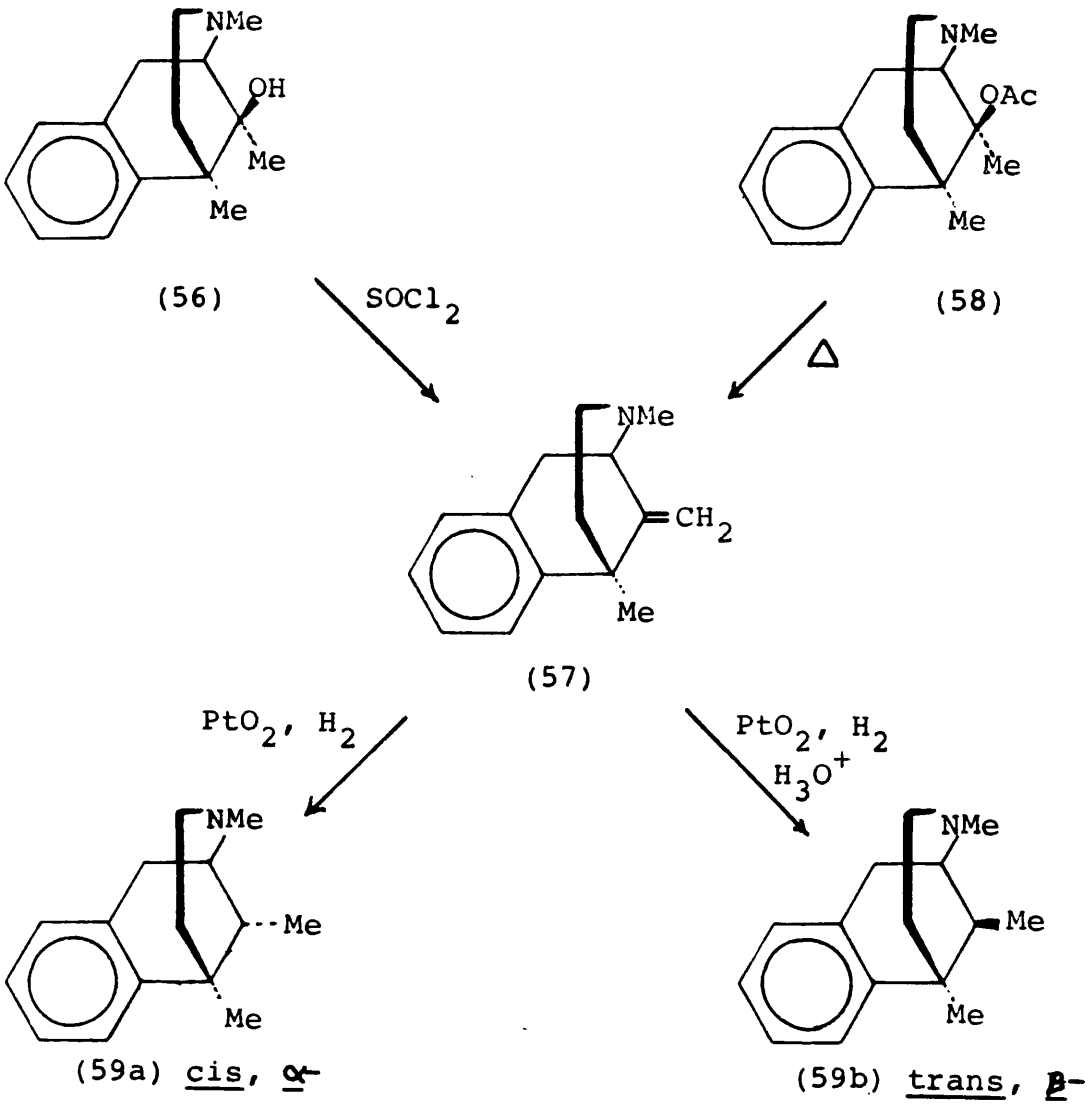


Figure 14

dequaternization, the 9β-hydroxybenzomorphan (54)[98]. Similar modes of addition occurred during Grignard or methyllithium[74,98] addition resulting in carbinol (55) with hydroxyl cis to the C_5-methyl, and carbinol (56) with hydroxyl trans to the C_5-methyl (Figure 14).

The mode of reaction was dependent on whether or not nitrogen was cationic. When nitrogen was cationic, addition to carbonyl occurred to yield the alcohol with hydroxyl oriented towards nitrogen. With neutral tertiary nitrogen, the epimeric alcohol was formed[99].



(59a) cis, α-

(59b) trans, β-

Figure 15

Thionyl chloride dehydration of 56 gave the 9-methylene-6,7-benzomorphan (57)[77]. Pyrolysis of the 9-acetyl-9-methyl benzomorphan (58) also gave the 9-methylene product (57). Hydrogenation of 9-methylene benzomorphan was stereoselective depending again upon the condition of the nitrogen atom[99] (Figure 15; 59a & 59b). The α- and β-isomers of the 9-hydroxymethyl-6,7-benzomorphan have been synthezised from the corresponding 9-methylene-6,7-benzomorphan (57) by hydroboration under controlled conditions[100], followed by peroxide oxidation.

Shiotani and Mitsuhasi[101] converted the 9-oxo-6,7-benzomorphan (60) into oxime (61), reduction of which demonstrated stereoselectivity (Figure 16). Hydrogenation of the oxime (61) in the presence of acetic acid and sulphuric acid gave 9β-acetamide (62) but in presence of only acetic acid it yielded 9α-acetamide (63).

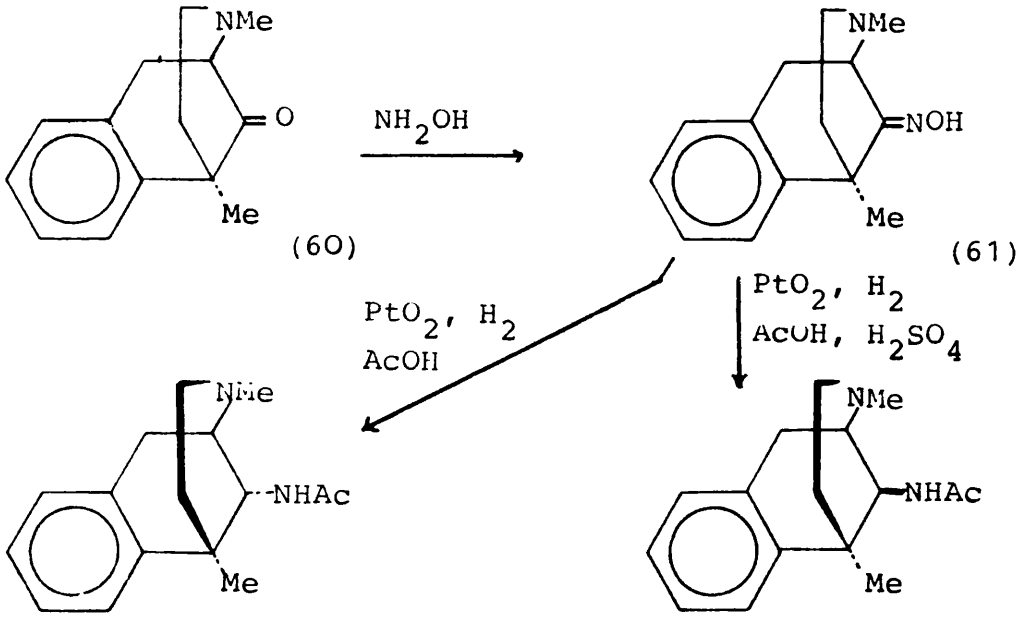
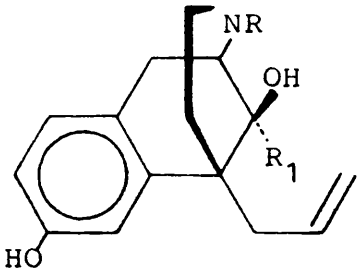


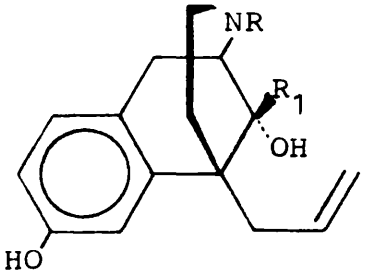
Figure 16

5-Allyl-9-oxo-6,7-benzomorphan and its methiodide salt were stereoselectively reduced to the corresponding 9β- and 9α-hydroxy compounds (64,65) respectively[102], which in turn were transformed to a number of 2-substituted-5-allyl-9-hydroxy-6,7-benzomorphans. A series of 3-hydroxy-8-oxaisomorphinans (66) and 3-hydroxy-8-oxamorphinans (67) were derived from the corresponding 9β- and 9α-hydroxybenzomorphans (64,65), respectively.



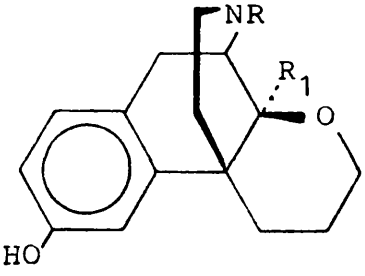
9β-OH

(64)

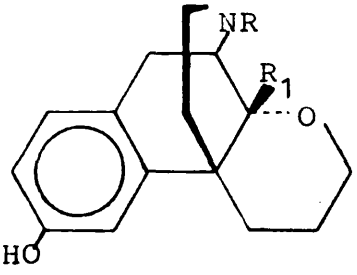


9α-OH

(65)



(66)

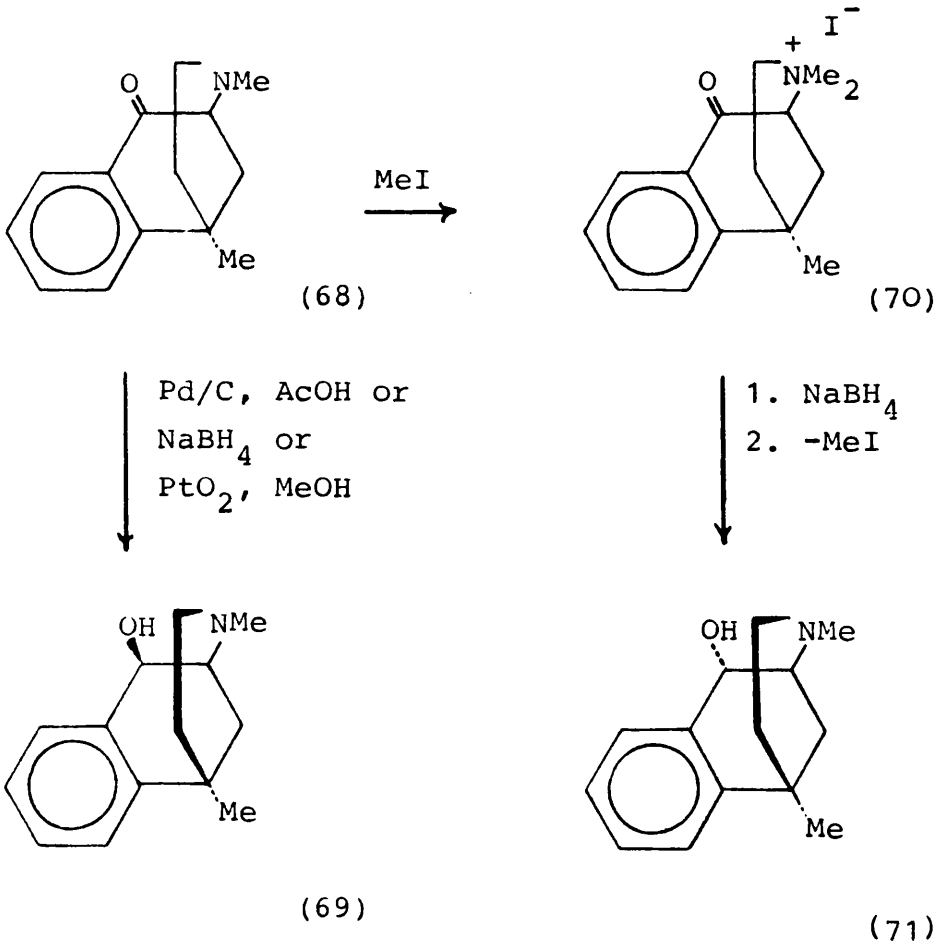


(67)

R_1 = H;

Figure 17

8-Oxobenzomorphans have provided a means of access to 8-hydroxy-6,7-benzomorphans and thence the acetyl derivatives. Catalytic reduction of the 8-oxo compound (68) with palladium-charcoal or platinium oxide gave only one and the same diastereomer[74] (69). Reduction of the ketone (68) with sodium borohydride also gave 8β-hydroxy-6,7-benzomorphan (69) whereas similar reduction of its methiodide (70) gave the 8α-hydroxy compound (Figure 18; 71)[103].



(68) (70) (69) (71)

Figure 18

The diastereomerically related 8α- and 8β-hydroxy-6,7-benzomorphans (77, 78) were prepared from 8-oxobenzomorphan[104] (72). Reduction of 8-oxobenzomorphan (72) with sodium borohydride yielded only the 2-methyl-8β-hydroxy diastereoisomer (73). The N-demethylated compound (74) was converted into the 2-tosyl derivative, which upon reduction and detosylation afforded exclusively 8β-hydroxy-6,7-benzomorphan (77). Conversion of 2-tosyl-8β-hydroxybenzomorphan (75) into the 2-tosyl-8β-tosyl derivative (76), followed by aqueous solvolysis and detosylation of the latter gave 8α-hydroxy-6,7-benzomorphan (Figure 19; 78).

Reaction of phenyllithium with the 2,5,9-trimethyl-8-oxo-6,7-benzomorphan (79) gave the 8,8-difunctionalized benzomorphan (80) which upon hydrogenolysis gave the 8α-phenyl derivative (Figure 20;81). Treatment of 79 with methyllithium afforded carbinol (82) which dehydrates with acid to the 8-methylene compound (83). Catalytic reduction of 83 gave 8α-methyl-6,7-benzomorphan[85] (Figure 20; 84).

Catalytic hydrogenation of the N-demethylated compound (85) afforded 8β-hydroxy-6,7-benzomorphan[105] (Figure 20; 86).

8-Oxobenzomorphan (72) was converted into the oxime which catalytically reduced in either acetic acid or acetic acid and sulphuric acid to give only 8β-acetamido-benzomorphan[101] (Figure 21; 87); this is in contrast to similar reduction of the oxime of 9-oxo-6,7-benzomorphan (refer to Figure 16; 61).

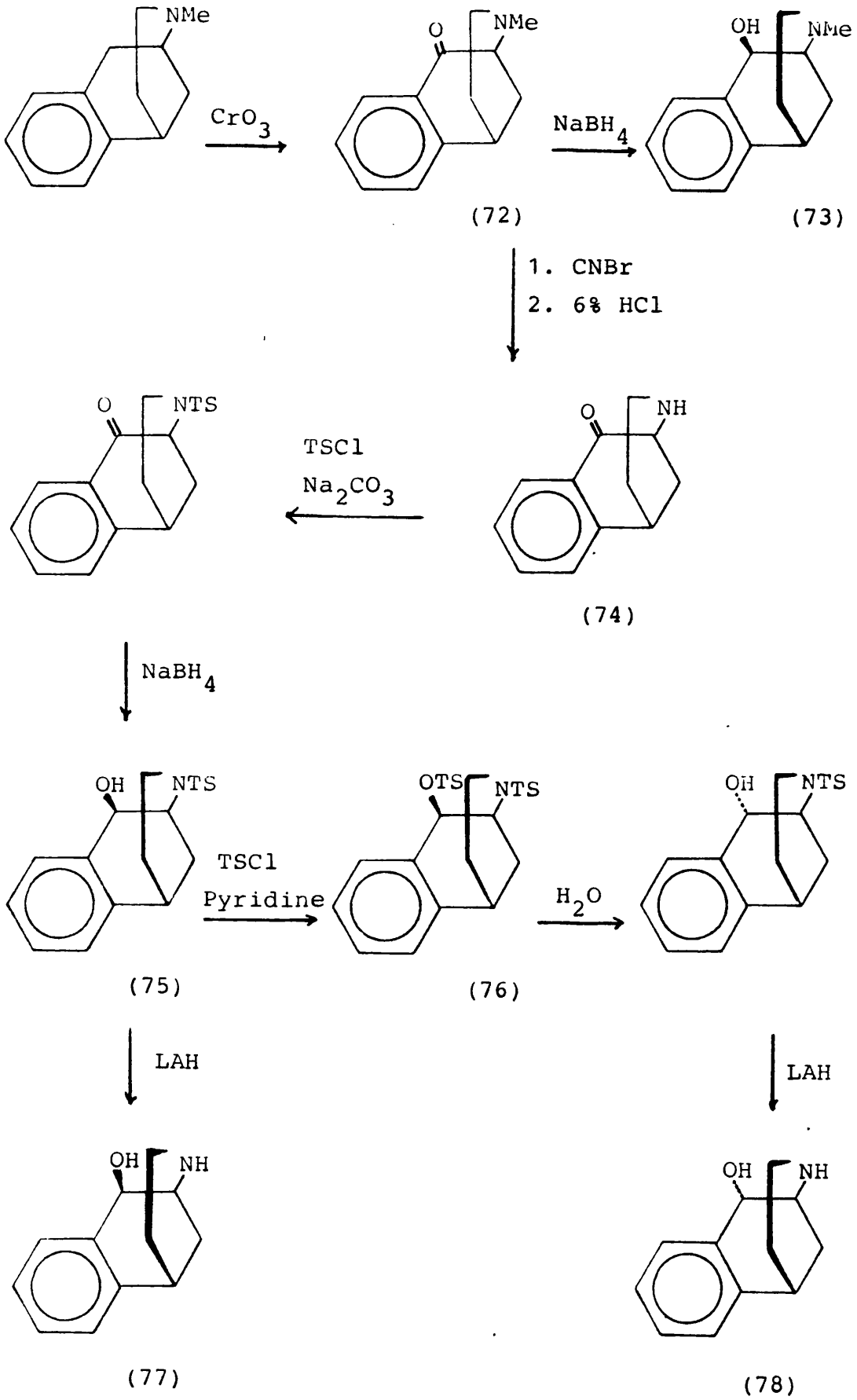

NMe
CrO_3
O
NMe
$NaBH_4$
OH
NMe
(72)
(73)
1. CNBr
2. 6% HCl
O
NTS
TSCl
Na_2CO_3
O
NH
(74)
$NaBH_4$
OH
NTS
TSCl
Pyridine
OTS
NTS
H_2O
OH
NTS
(75)
(76)
LAH
LAH
OH
NH
OH
NH
(77)
(78)

Figure 19

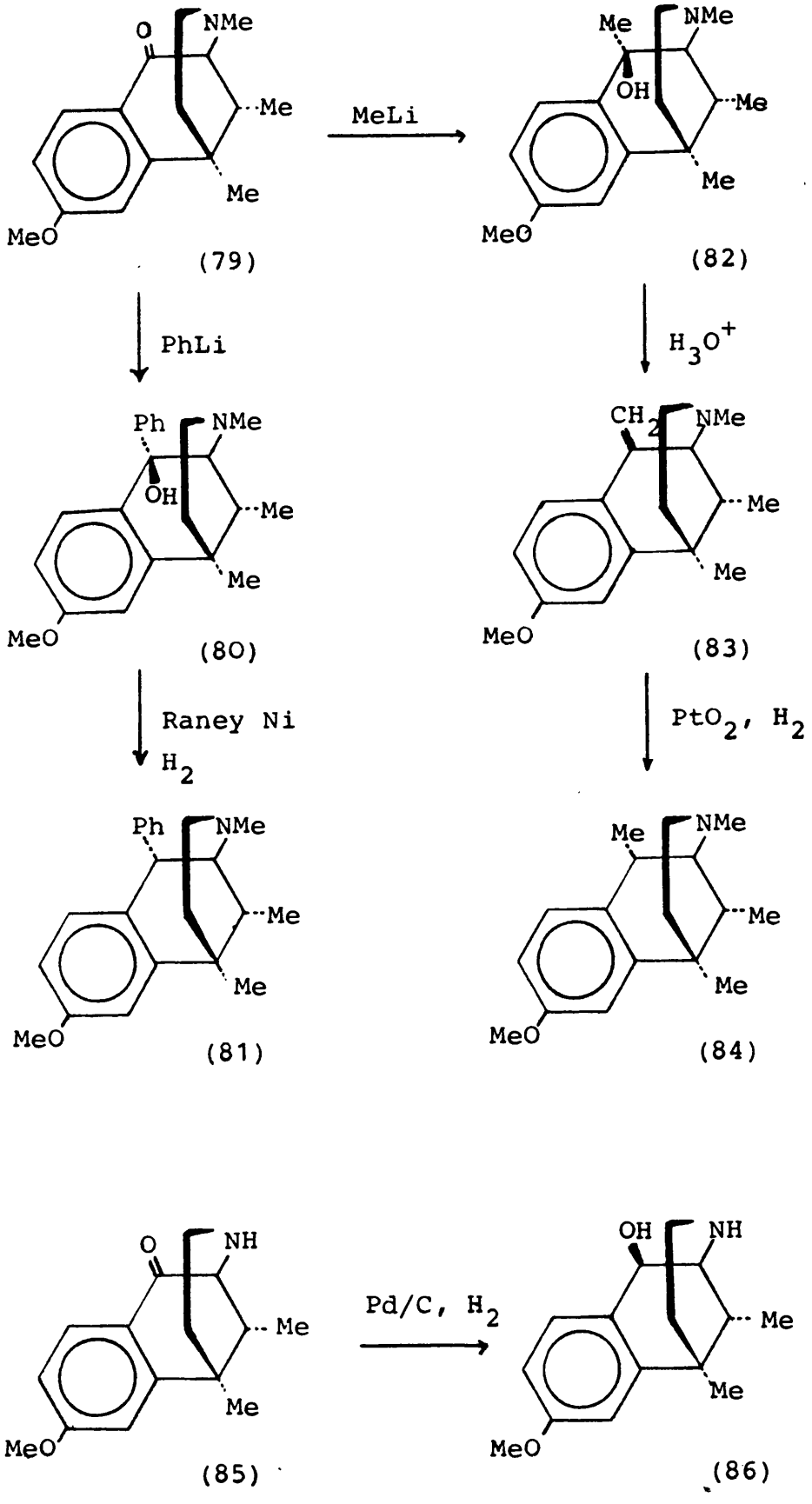
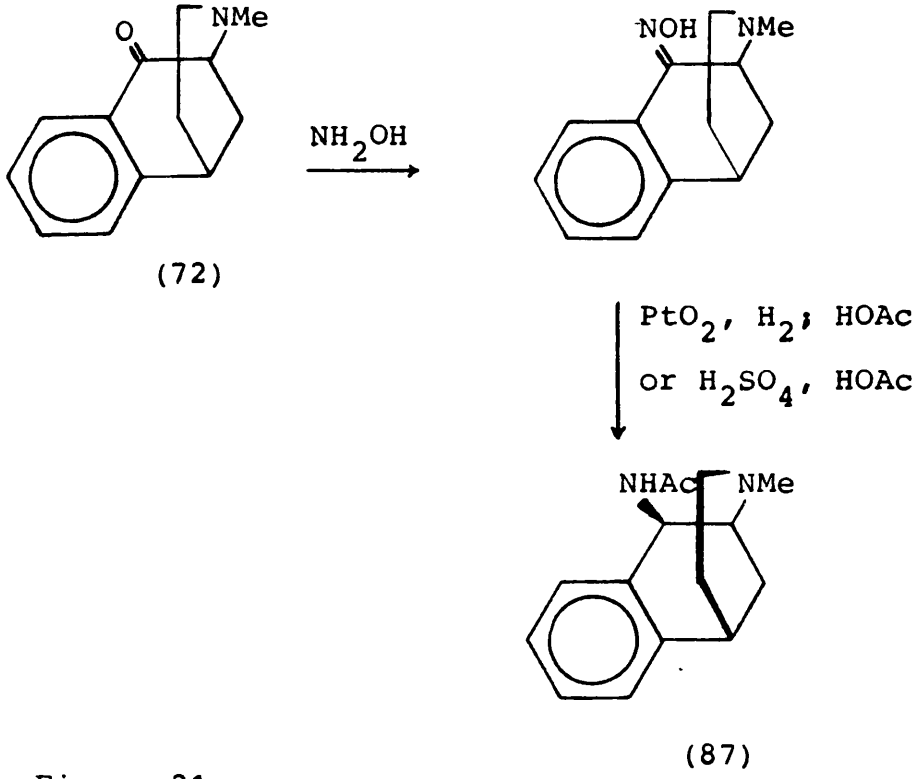

O
NMe
Me
Me
MeO
(79)
MeLi
Me
NMe
OH
Me
Me
MeO
(82)
PhLi
H_3O^+
Ph
NMe
OH
Me
Me
MeO
(80)
CH2
NMe
Me
Me
MeO
(83)
Raney Ni
H_2
PtO_2, H_2
Ph
NMe
Me
Me
MeO
(81)
Me
NMe
Me
Me
MeO
(84)
O
NH
Me
Me
MeO
(85)
Pd/C, H_2
OH
NH
Me
Me
MeO
(86)

Figure 20



(72)

(87)

Figure 21

Treatment of the 2,5-dimethyl-8-oxo-6,7-benzomorphan (Figure 22; 88) with lithium-ethylacetate, followed by dehydration with thionyl chloride-pyridine gave the 8-ethoxycarbonylmethylene compound (89). Catalytic hydrogenation of 89 gave the 8β-ethoxycarbonylmethyl isomer (90) which, after demethylation, was cyclized to give the lactam (91). The lactam was reduced with LAH, and O-demethylated to give the 2,8-bridged benzomorphan (92).

Treatment of ketone (93) with ethyl bromoacetate, followed by reduction with sodium borohydride yielded the diol (94), which was cyclized by treatment with HCl-ethanol to give compound (95)[106].

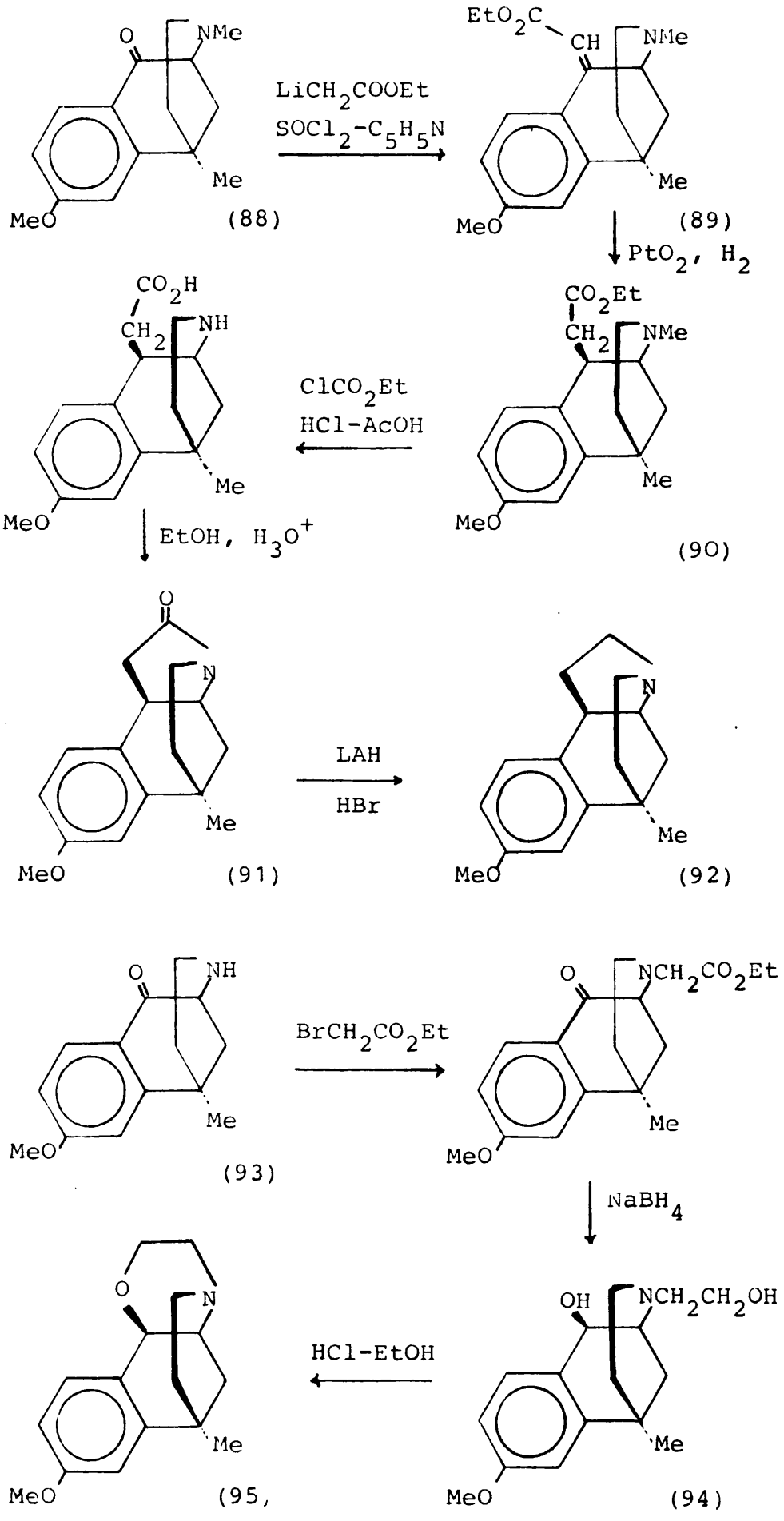

LiCH2COOEt
SOCl2-C5H5N
PtO2, H2
ClCO2Et
HCl-AcOH
EtOH, H3O+
LAH
HBr
BrCH2CO2Et
NaBH4
HCl-EtOH
(88)
(89)
(90)
(91)
(92)
(93)
(94)
(95)

Figure 22

PART TWO

DISCUSSION

CHAPTER TWO

SYNTHESIS AND REACTIONS OF BENZOMORPHANONES

CHAPTER TWO

SYNTHESIS AND REACTIONS OF BENZOMORPHANONES.

2.0 Introduction.

The substitution of a carbon-bonded hydrogen by a carbonyl oxygen atom is one of the more useful chemical reactions available for 'functionalizing' a carbon atom thereby making it available for reaction with a variety of chemical reagents.Many agents are available for the oxidation of organic compounds[107], among the most commonly employed are derivatives of chromium or manganese.

May et al[74] have prepared 2,5-dimethyl-8-oxo-6,7-benzomorphan (100) in about 5% yield from hydrotropanitrile (Figure 7:, page 42). 8-Oxo-6,7-benzomorphans have been prepared by other methods[77,78] (figures 8 and 9). The direct introduction of oxygen at the benzylic position in previously prepared benzomorphans has been achieved by chromium trioxide oxidation in either aqueous sulphuric acid or acetic anhydride. Ziering et al[85] oxidized 2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan with chromium trioxide in sulphuric acid to give the corresponding 8-ketone in good yields. 2-Methyl-8-oxo-6,7-benzomorphan was prepared by Fauley et al[104] with chromium trioxide in acetic anhydride in 70% yield.

The most effective method for performing the oxidation of the benzylic carbon of 6,7-benzomorphans is

described in this chapter. The simple procedure involved the use of an excess of a stirred dilute solution of chromium trioxide in acetic acid at room temperature. Various other oxidising agents, which are known to attack benzylic methylene groups were also investigated (Section 2.1).

8-Oxo-6,7-benzomorphans may be converted into the corresponding nitriles by reaction with tosylmethyl isocyanide (TOSMIC) in the presence of base[108]. TOSMIC adds one carbon to a ketone as in the cyanohydrin reaction but without the simultaneous formation of an α-hydroxy group. Clearly the nitrile is a useful synthetic intermediate which may by further exploited, for instance, by conversion into the carboxylic acid and derivatives. The oximes (117 & 119) of 8-oxobenzomorphans were prepared in good yield by standard method.

A search of the literature revealed that no compounds in the benzomorphan series possessing halogen at C-8 have been reported. The halogenation of benzomorphan is an attractive synthetic step since the resulting halide may prove to be a useful synthetic intermediate. Amines, for example, may be prepared by the reaction between alkyl halide and potassium phthalimide to give N-alkyl phthalimide which may be cleaved to afford the corresponding primary amine. The classical procedure for displacement of halogen by cyanide is well known[128,129]. An attempt was made therefore to synthesise 2,5,9-trimethyl-8-bromo-6,7-benzomorphan.

2.1 Synthesis of 2,5-dimethyl-6,7-benzomorphan and 2,5,9-trimethyl-6,7-benzomorphan.

The Grewe synthesis of 6,7-benzomorphans involves an acid-catalyzed cyclization of appropriately substituted tetrahydropyridines. The Grignard reagent derived from benzyl chloride was reacted with 4-picoline methiodide to give the unstable dihydropyridine (96) which was immediately reduced by sodium borohydride in almost quantitative yield. The tetrahydropyridine (97) formed was cyclized with 48% hydrobromic acid (HBr) to give 2,5,dimethyl-6,7-benzomorphan[20,93] (Figure 23; 40).

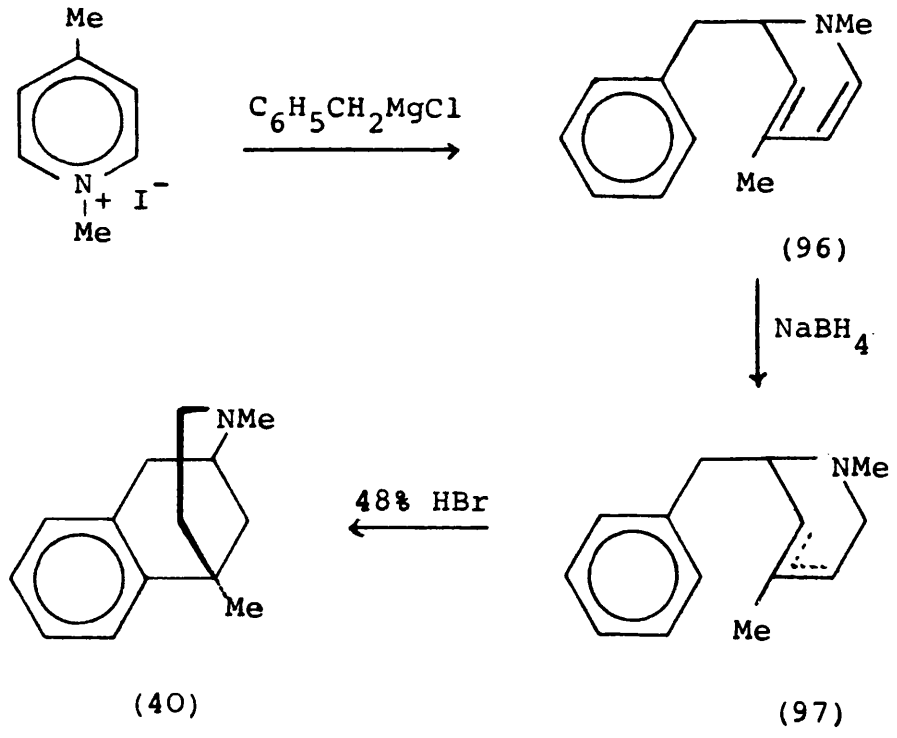
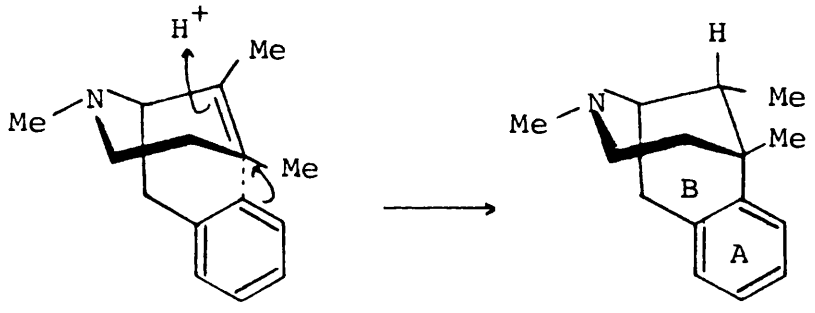


Figure 23

2.1.1 2,5,9-Trimethyl-6,7-benzomorphan (99)[87] was obtained in a similar manner from 3,4-lutidine. The predominant α-diastereoisomer was isolated as the hydrochloride salt. In the α-isomer the C-9 methyl has a higher proton magnetic resonance (PMR) chemical shift than that of β, and this has been interpreted in terms of a diamagnetic shielding of the α C-9 methyl by the fused benzene ring[93].

In the Grewe synthesis, the major product is always that in which alkyl groups are cis with respect to hydroaromatic ring B (Figure 24; 99). This is expected if cyclization is viewed as a trans addition to the double bond of the tetrahydropyridine (98); protonation occurs from the less hindered side[109] (Figure 24).

Optical resolution of the enantiomeric pairs has shown that the biological activity resides mainly in the leavo isomer. Resolution can be effected by (+) -3 bromo-8-camphorsulphonic acid[93] or with a combination of (+)- and (-)- mandelic acid[31,32]. No separation of optical isomers was attempted.

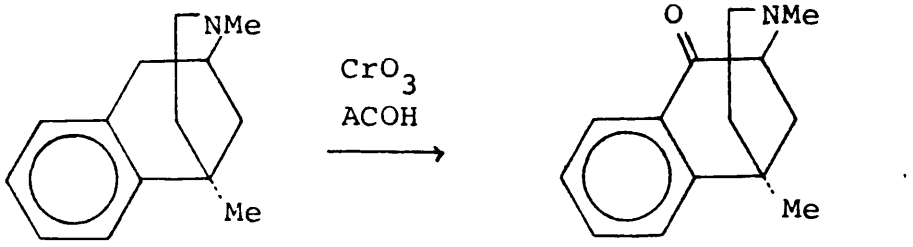


(98) (99)

Figure 24

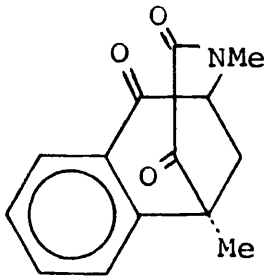
2.2 Synthesis of 2,5-dimethyl-8-oxo-6,7-benzomorphan (100) and 2,5,9-trimethyl-8-oxo-6,7-benzomorphan (115).

The 2,5-dimethyl-6,7-benzomorphan was oxidized with chromium trioxide in aqueous acetic acid to give 2,5-dimethyl-8-oxo-6,7-benzomorphan (100). Chromic acid in 95% aqueous acetic acid was added dropwise to the solution of 6,7-benzomorphan in glacial acetic acid over a period of several hours. Efficient stirring was required for an optimum yield of the 8-oxobenzomorphan (100). When addition was complete the reaction was stirred at room temperature for an additional 20 hours. The solution was then poured into ice cold water, basified and the products isolated by ether extraction.



(100)

+

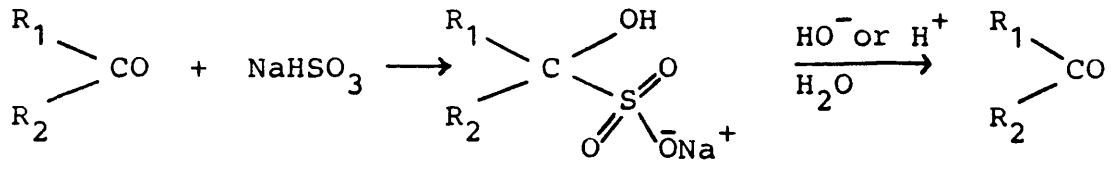


(101)

Figure 25

This procedure gave a mixture of products as indicated by thin layer chromatography (silica, MeOH: DCM:ACOH 12:4:1). The main product required was the ketone (100) but some 2,5-dimethyl-3,4,8-trioxo-6,7-benzomorphan (101) and unreacted starting material were also isolated. The trioxo compound (101) was separated from the resulting mixture through its lower solubility in nonpolar solvents such as cyclohexane and petroleum ether. The infra-red spectrum of the trioxo-6,7-benzomorphan (101) exhibits absorption at ν_{max} 1690cm^{-1} and 1730cm^{-1} due to carbonyl functionalities. The PMR spectrum shows nine aliphatic protons (1.8-4.0 ppm). The C-5 methyl appears as a singlet at 1.84 ppm while the N-methyl resonates at 3.1 ppm as expected. The remainder of the aliphatic protons, C_1 and C_9, resonate at 3.98 ppm (t) and 2.67 ppm (d) respectively. The molecular ion observed at M/Z 243 by mass spectrometry supports structure (101).

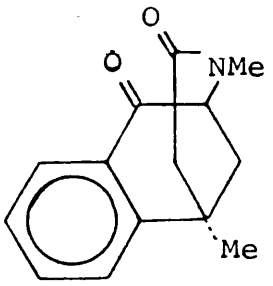
Purification of 8-oxobenzomorphan (100) was achieved by passing the crude material through a silica column (12:4:1 , MeOH;DCM:ACOH). It may also be purified via the bisulphite addition compound (102) or the oxime derivative (117).



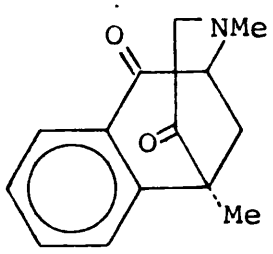
(102)

Absorption at ν_{max} 1680 cm^{-1} in the infra-red spectrum of the product (100) suggested a conjugated carbonyl group. The melting point and spectral data confirmed the structure of the 8-oxo-6,7-benzomorphan (100).

It is interesting that no dioxo compounds (103 or 104) were detected. This suggests that attack at carbon 3 and 4 occurs almost simultaneously. Oxidation at one of the methylene positions probably increases the susceptibility of the adjacent carbon to oxidation.



(103)



(104)

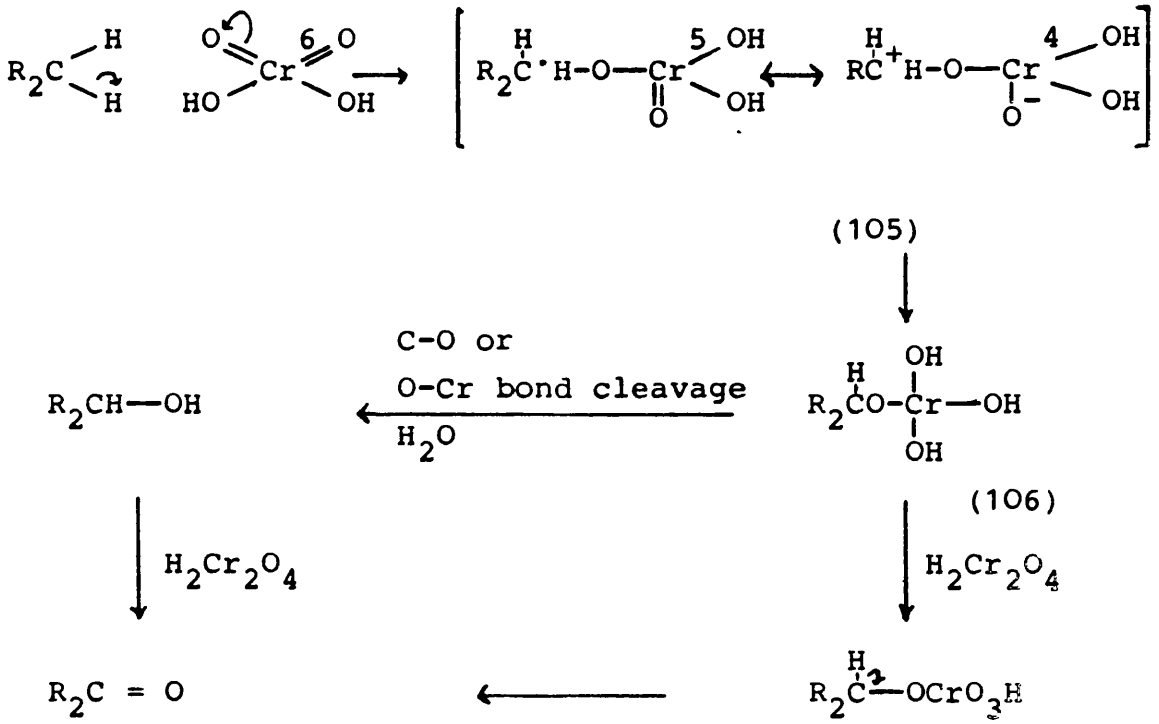
The relative rates of oxidation of primary, secondary and tertiary hydrogens are 1:110:7000[107]. With 6,7-benzomorphans reaction at the tertiary C-H bond at the bridgehead is suppressed because of the increase in strain associated with a change in hybridization at that position. The C_9 methylene bridge is not attacked, presumably because of the increase in strain resulting from a change in hybridization.

The yield of 8-oxobenzomorphan (100) was optimised by varying the concentration of the reactants employed,

the reaction time and reaction temperature. At elevated temperatures it was found to give higher yields of the trioxobenzomorphan (101). The time course of this oxidation which was followed by thin layer chromatography showed an initial rapid phase, followed by a slowing and finally cessation of reaction with oxidizing agent still remaining. The decrease in the rate of reaction with increasing time is possibly due to the production of acetate ion during the reaction. Acetate is known to retard oxidation reactions[113]. Chromic acid oxidation at the benzylic position in aqueous acetic acid is accelerated by increasing the concentration of mineral acid[111].

The mechanism of the chromic acid oxidation has been extensively studied[107]. The observation of a kinetic isotope effect demonstrates that the cleavage of the carbon-hydrogen bond occurs in the rate-determining step. Oxidation of aromatic side chains is believed to be initiated by attack at a benzylic C-H bond[112]. A possible mechanism for chromic acid oxidations is outlined in Scheme 1. The initial step involves either a hydride ion (two electron transfer) or a hydrogen atom abstraction (one electron transfer, as illustrated). Rocek[112] has proposed that the transition state for hydrogen transfer is a resonance hybrid (105), in which the carbon atom has both radical and carbonium ion character. This then reacts with the chromium derivative to form the chromium (1V) ester

(106) which is generally regarded as the reaction intermediate which leads to the observed products. The benzylic type radical, the initial species involved in the oxidation of 6,7-benzomorphans, is expected to form only slowly due to difficulty in its stabilisation through overlap of the Sp^2 hybridised C-8's p-orbital with the aromatic ring, a conclusion supported by examination of molecular models.

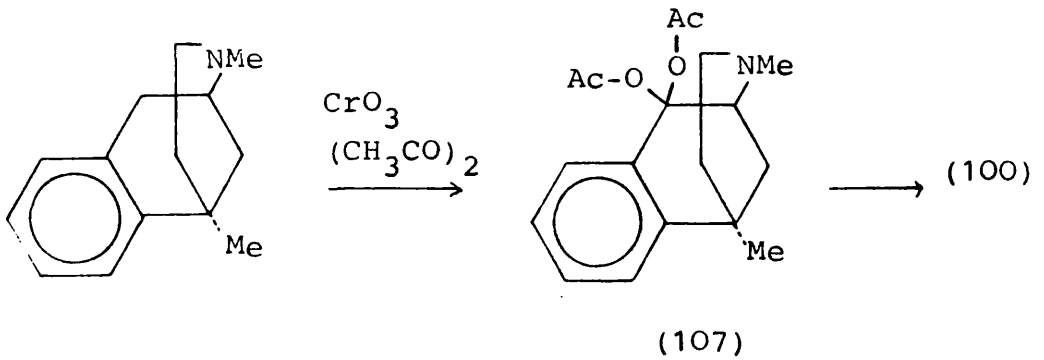


Scheme 1

Oxidation by chromium trioxide varies with the nature of chromium (1V) species employed but solvent also has a marked effect on the rate and the type of reaction which occurs. The use of chromium acetate for such reactions was first reported by Thiele and Winter[107]. They

found that the oxidation of several substituted toluenes with chromium trioxide in acetic anhydride in the presence of a strong acid gave good yields of the benzal diacetates (eg. 108).

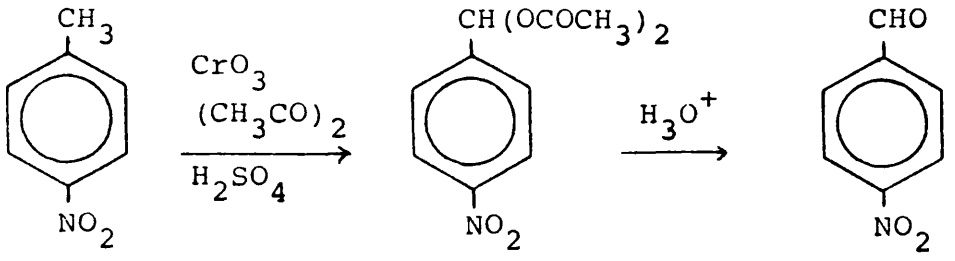
The oxidation of 6,7-benzomorphans with chromyl acetate was examined in some detail. Chromyl acetate solution was prepared by adding the chromium trioxide to the acetic anhydride slowly with cooling and stirring. The benzomorphan (40) was dissolved in acetic anhydride at $0^{o}C$ and concentrated sulphuric acid was added slowly. When the mixture had cooled to $0^{o}C$ chromyl acetate solution was added at such a rate that the temperature did not exceed $6^{o}C$ and stirring was continued at this temperature for several hours. The brownish oil isolated was identified as diacetate derivative (Figure 26; 107). An absorption peak at ν_{max} 1685 cm^{-1} ($\diagdown$C=O), 1740 cm^{-1} ($\diagdown$C=O) and 1230 cm^{-1} (-C(=O)-O-) in the infrared spectrum, together with PMR spectrum support structure (107) as the product. The diacetate was then hydrolysed with sulphuric acid in 50% ethanol to give 8-oxobenzomorphan (100) in a poor yield (below 8%).



(107)

Figure 26

Chromyl acetate is generally quite satisfactory for converting toluene derivatives to the corresponding aldehyde. The success of this procedure has been attributed to the formation of the diacetate (eg. 108) which is resistant to further oxidation. The reaction of aromatic aldehydes with acetic anhydride in the presence of acid occurs much more rapidly than the oxidation of the aldehyde. This then provides a route for the protection of aldehyde as it is formed[107].



(108)

Carr[114] has reported oxidation of 2,5-dimethyl-6,7-benzomorphan (40) with acidic chromic acid solution. His procedure gave a lower yield of 8-oxo compound (100) than the oxidation with chromium trioxide in acetic acid largely due to incomplete oxidation. A further disadvantage of this method is that it required drastic conditions which included refluxing the solution of benzomorphan in acidic chromic acid.

Other oxidizing agents which are known to oxidise benzylic methylene groups were also investigated. Hydrogen-transfer reactions between phenols and high-

potential quinones can lead to a wide variety of products[115]. The process may be controlled to allow selective benzylic oxidation of suitable phenols by the use of alcoholic solvents[116] (Figure 27). Quinone methides (eg. 110) formed by dehydrogenation are thought to be intermediates in these reactions, and stable forms of these species have been isolated as the end products of suitable blocked and hindered phenols[117]. Benzylic oxidation of phenols by 2,5-dichloro-5,6-dicyanobenzoquinone (109) does not require protection of the phenolic hydroxyl group, whereas chromic acid oxidation of aromatic compounds of this type are readily oxidized to quinones.

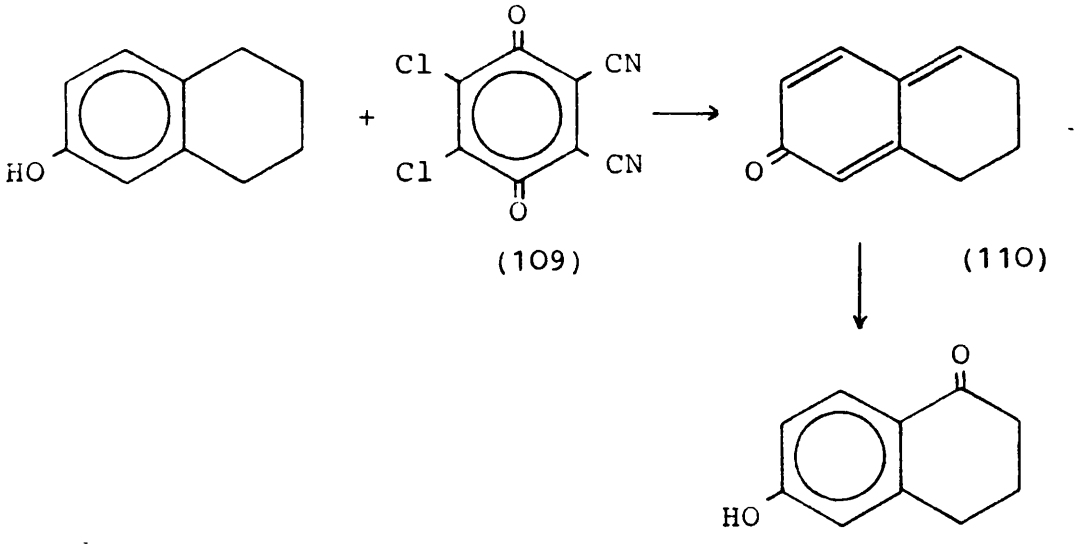


Figure 27

Oxidation of 2'-hydroxy-2,5-dimethyl-6,7-benzomorphan (Figure 28; 111) with 2.0 equivalents of dichlorodicyanoquinone in methanol gave a two component mixture, one of which was unreacted starting material. The minor component

was identified as 8α-methoxy-6,7-benzomorphan (113) from its spectral properties. No trace of the corresponding 8-oxo-6,7-benzomorphan (114) was detected. An IR spectrum did not show the carbonyl bond. The PMR spectrum obtained for product (113) showed a singlet at 3.47 ppm due to methoxy and the normal benzylic protons signal at ~3.2 ppm was absent. A new downfield singlet was evident at 4.75 ppm due to the 8β benzylic proton. Mass spectral evidence supported the proposed structure for (113). The formation of 8α-methoxy-6,7-benzomorphan is rationalized by the mechanism outlined in Figure 28. It is proposed that this product arises by addition of alcohol to the reactive quinone methide intermediate (112) and represents the halfway stage in the oxidation process.

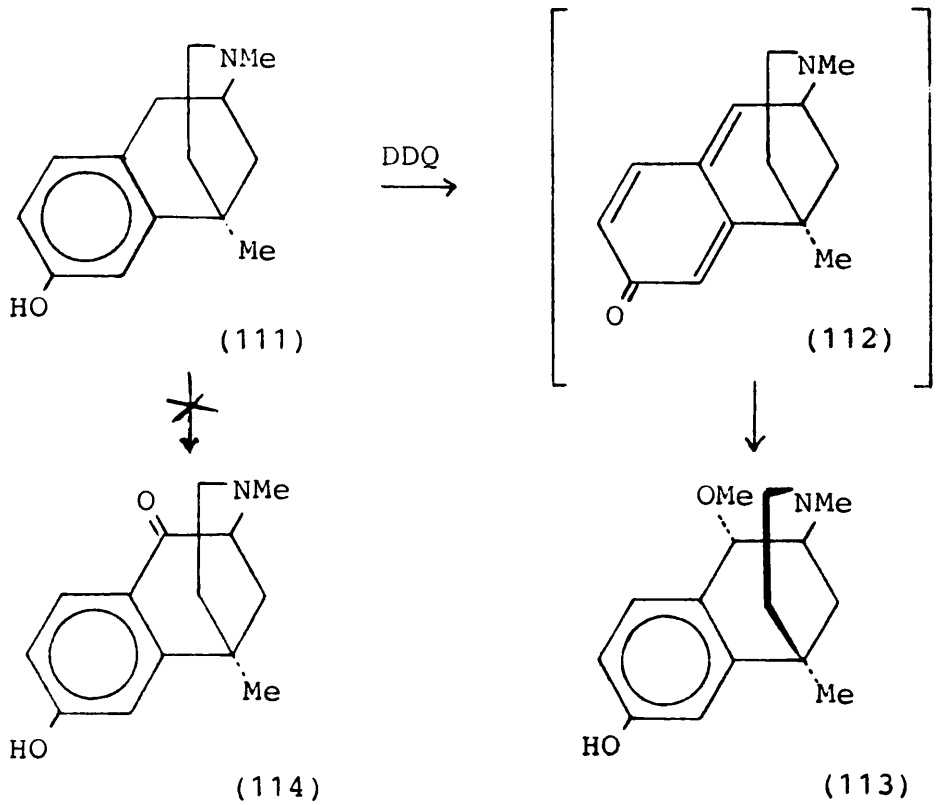
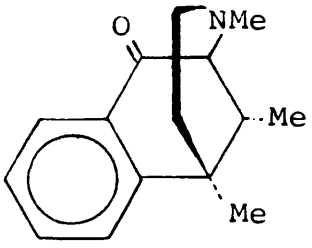


Figure 28

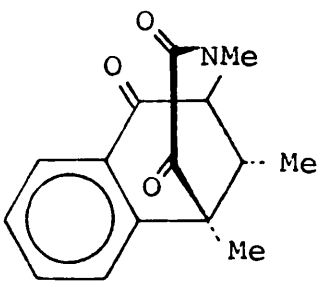
Several attempts were made to oxidize 111 with dichlorodicyanoquinone by varying the concentration of the reactants employed, temperature and the reaction time. In most cases, low yields of 8-methoxy derivative (113) were obtained.

The use of cerium (IV) ammonium nitrate[118] or silver nitrate ammonium persulphate[119] to oxidize 2,5-dimethyl-6,7-benzomorphan (40) was ineffective and unreacted starting material was recovered in each case. Ethyl benzene and tetralin are known to give acetophenone and 1-tetralone respectively in 76-78% yield when treated with ceric ammonium nitrate in 3.5 M nitric acid.

2.2.2 Similarly 2,5,9-trimethyl-6,7-benzomorphan (99) was oxidized by chromium trioxide in 95% aqueous acetic acid to the corresponding 8-oxo-6,7-benzomorphan (115) in good yields. Oxidation of this benzomorphan required careful, slow addition of chromium trioxide solution in acetic acid over a longer time compared



(115)

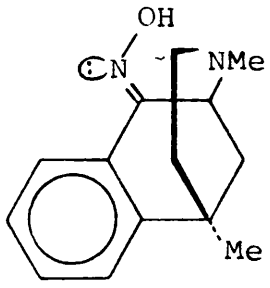


(116)

with 2,5-dimethyl-6,7-benzomorphan. The side product, trioxo compound (116), was formed in a larger quantity than in the case of 2,5-dimethyl-6,7-benzomorphan but no dioxo compounds were detected.

2.3 Synthesis of 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime (117) and 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime (120).

The oxime derivative (117) was prepared by heating the 8-oxo-6,7-benzomorphan (100) and hydroxylamine hydrochloride in boiling ethanol for 18 hours. The hydroxylamine salt was neutralized by addition of sodium acetate, which also provided a buffering action near the optimum pH for condensation. Although this reaction is reversible the equilibrium favours condensation under the experimental condition employed. Since water is one of the products of the reaction, the use of anhydrous systems is advantageous. Removal of water from the reaction medium to force condensation was unnecessary.



(117)

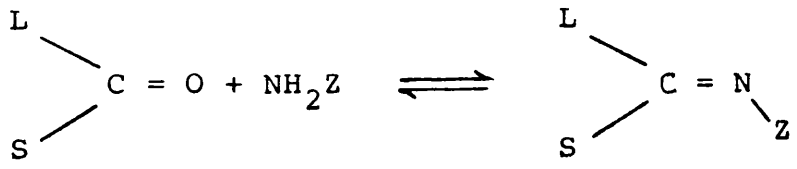
Carbonyl compounds usually react completely with free hydroxylamine (equation A) but the instability of free hydroxylamine due to air oxidation often discourages its use. On the other hand, although hydroxylamine hydrochloride is relatively stable, an equilibrium is involved in its reaction with carbonyl compound (equation B). The condensation of the 8-oxo-6,7-benzomorphan and free hydroxylamine (NH_2OH) was carried out by heating the reactants in methanol. A solution of free hydroxylamine was prepared from $NH_2OH.HCl$ and sodium acetate in methanol. After one hour, the mixture was filtered and the filtrate was treated with 8-oxo-6,7-benzomorphan (100). This procedure was found to give an improved yield of oxime (117).

$$\text{>C = O} + NH_2OH \longrightarrow \text{>C = NOH} + H_2O \qquad \text{(A)}$$

$$\text{>C = O} + NH_2OH.HCl \rightleftharpoons \text{>C = NOH} + H_2O + HCl \qquad \text{(B)}$$

All ketones which have two different groups attached to the carbonyl carbon are capable of affording two isomeric oximes. However, as a rule, one of the isomers is formed in a great excess over the other. NMR studies of solutions of semicarbazones and phenylhydrazones show that condensation gives rise exclusively to the isomer in which the bulky Z group attached to the imino nitrogen bears a <u>syn</u> relation-

ship to the smaller S group[120].



syn

The condensation of the 8-oxo-6,7-benzomorphan and hydroxylamine gave rise exclusively to the ketoxime (117) isomer which bears a syn relationship to the bridgehead carbon (C_1). This was deduced from the deshielding effect experienced by the bridgehead proton by the proximity of the hydroxyl group. The chemical shift of that proton depends upon whether it is syn or anti to the hydroxyl group; when syn it is deshielded[120,121]. The main deshielding effect is regarded as arising from the proximity of the unshared pair of electrons on nitrogen[122], however Huitric et al[123] have presented evidence for the greater effect being due to the proximity of the hydroxyl oxygen non-bonding electrons. The chemical difference in the hydroxyl proton resonance of the oxime is also useful for assignment of configuration[124].

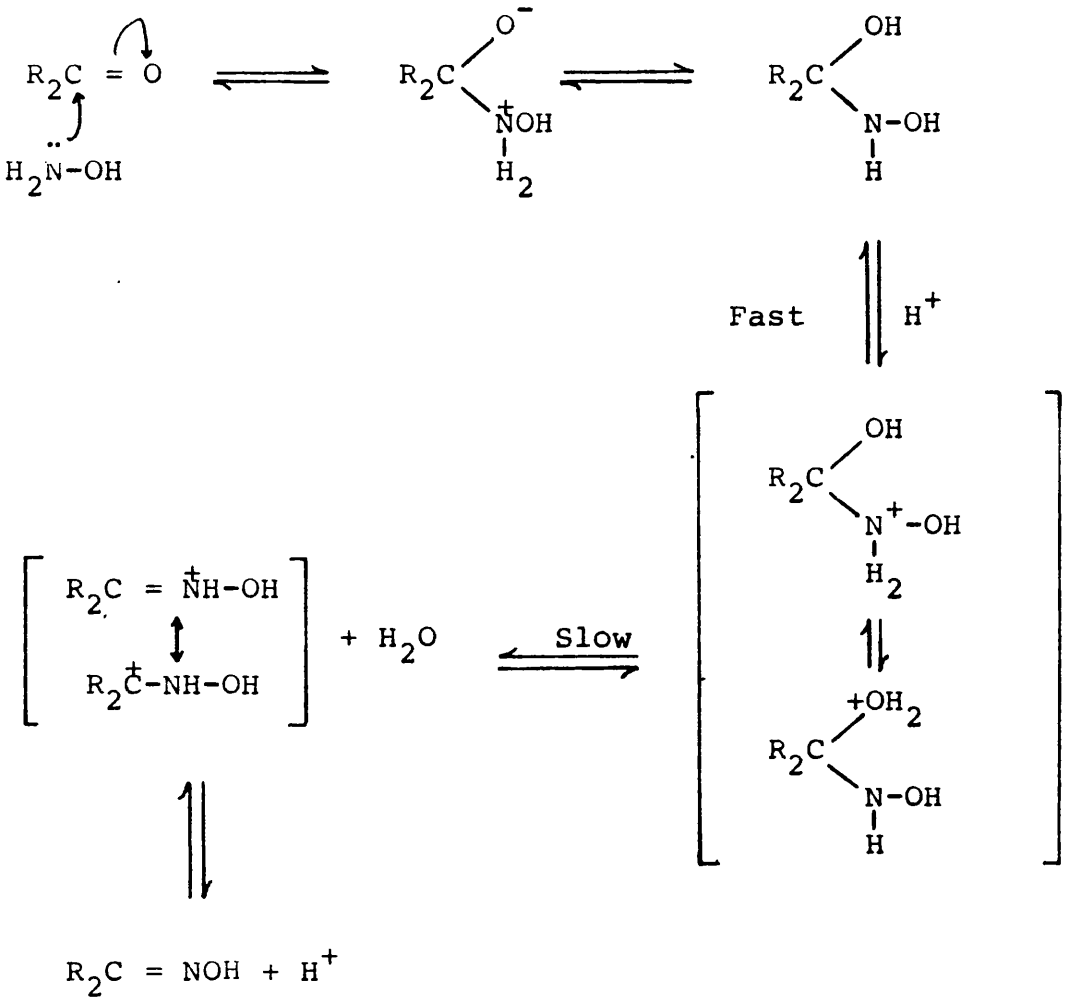
The PMR spectrum obtained for the oxime (117) shows the bridgehead C_1-proton resonates at 4.41 ppm (t); this is at a considerably lower field when compared with the corresponding 8-oxobenzomorphan (100; ~3.0 ppm,t).

The formation and hydrolysis of oximes has been

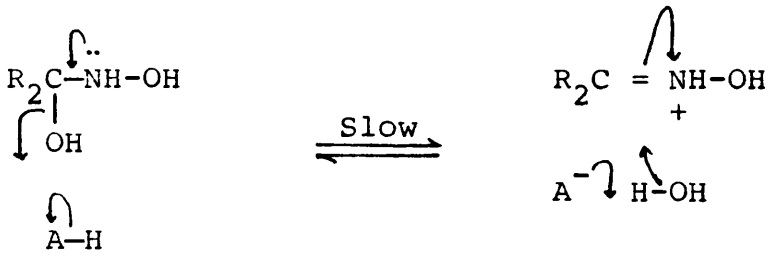
the subject of a number of investigations[110,125,126]. Reactions tend to exhibit general acid catalysis and it is established that in the formation reaction the addition step is rapid in comparison to the dehydration step. The acid catalysis of hydroxylamine condensation with a ketone in neutral solution involves catalysis of the dehydration step and not the facilitation of addition by conversion of the carbonyl compound into its conjugate acid.

The observation that the reactions show pH optima is mainly due to transitions in the rate determining stages with changing acidity of the reaction medium. At pH 7 the addition step is fast and in this region the overall rate increases with increasing acidity, the acid-catalysed dehydration being now rate-determining. When the acidity is increased, the addition step becomes gradually slower owing to the conversion of the nitrogen base into its conjugate acid, and at sufficiently high acidities this will determine the overall rate. A possible mechanism for such condensation reactions is outlined in Scheme 2.

The dehydration of the carbinolamines and the addition of water to oximes are subject to both specific and general acid catalysis. The addition of hydroxylamine to a carbonyl group also exhibits some specific acid catalysis[125,126].



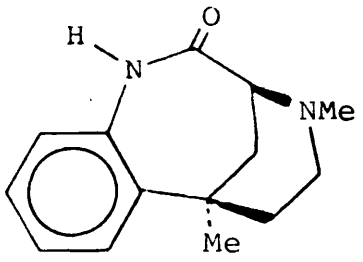
Specific acid catalysis.



General acid catalysis.

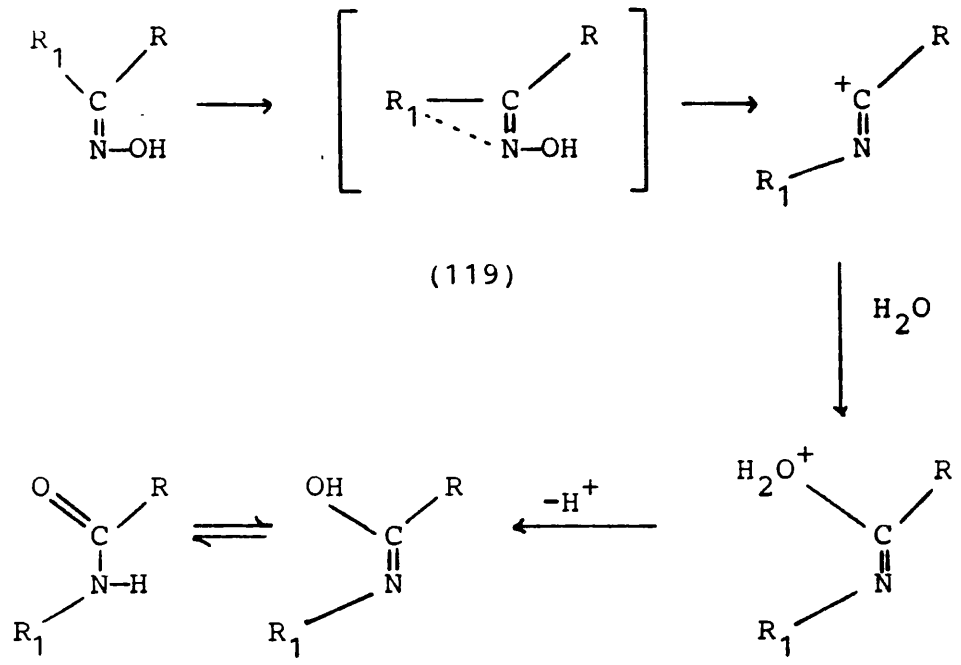
Scheme 2

Beckmann rearrangement of the oxime (117) was carried out by treating it with polyphosphoric acid at 150°C. This gave a single product whose IR and PMR spectra suggested that, in agreement with previous literature reports[98], it had the acylanilide-type lactam structure (118) rather than the alternative benzamide-type lactam structure, and this confirmed the assignment of the ketoxime (117).



(118)

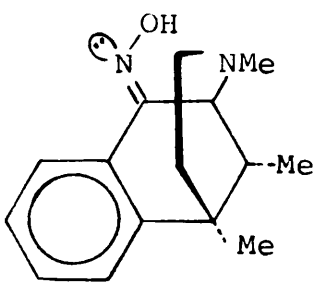
In the Beckmann rearrangement, the group which migrates is usually <u>trans</u> (ANTI) to the hydroxyl function, and this is often used as method of determining the configuration of the oxime[127]. Concerted fission and rearrangement is necessary to explain the stereochemistry, and species (119) is generally assumed to be a transition state or intermediate (Scheme 3).



(119)

Scheme 3

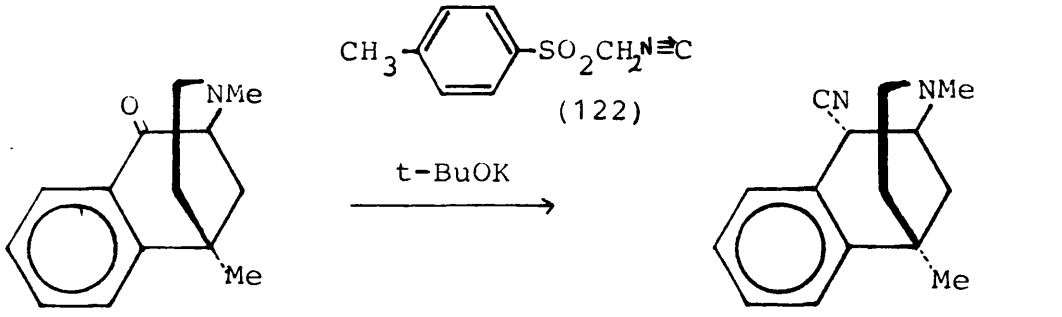
2.3.2 Similarly 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime (120) was prepared from the corresponding 8-oxo-6,7-benzomorphan (115). Only one ketoxime isomer was isolated and this was found to bear a syn relationship to the bridgehead carbon$_1$. The PMR spectrum of the oxime shows the C_1-proton as doublet at 4.22 ppm. The C_1-proton is strongly deshielded apparently due to the proximity of the hydroxyl group.



(120)

2.4 The synthesis of 8-cyano-2,5-dimethyl-6,7-benzomorphan.

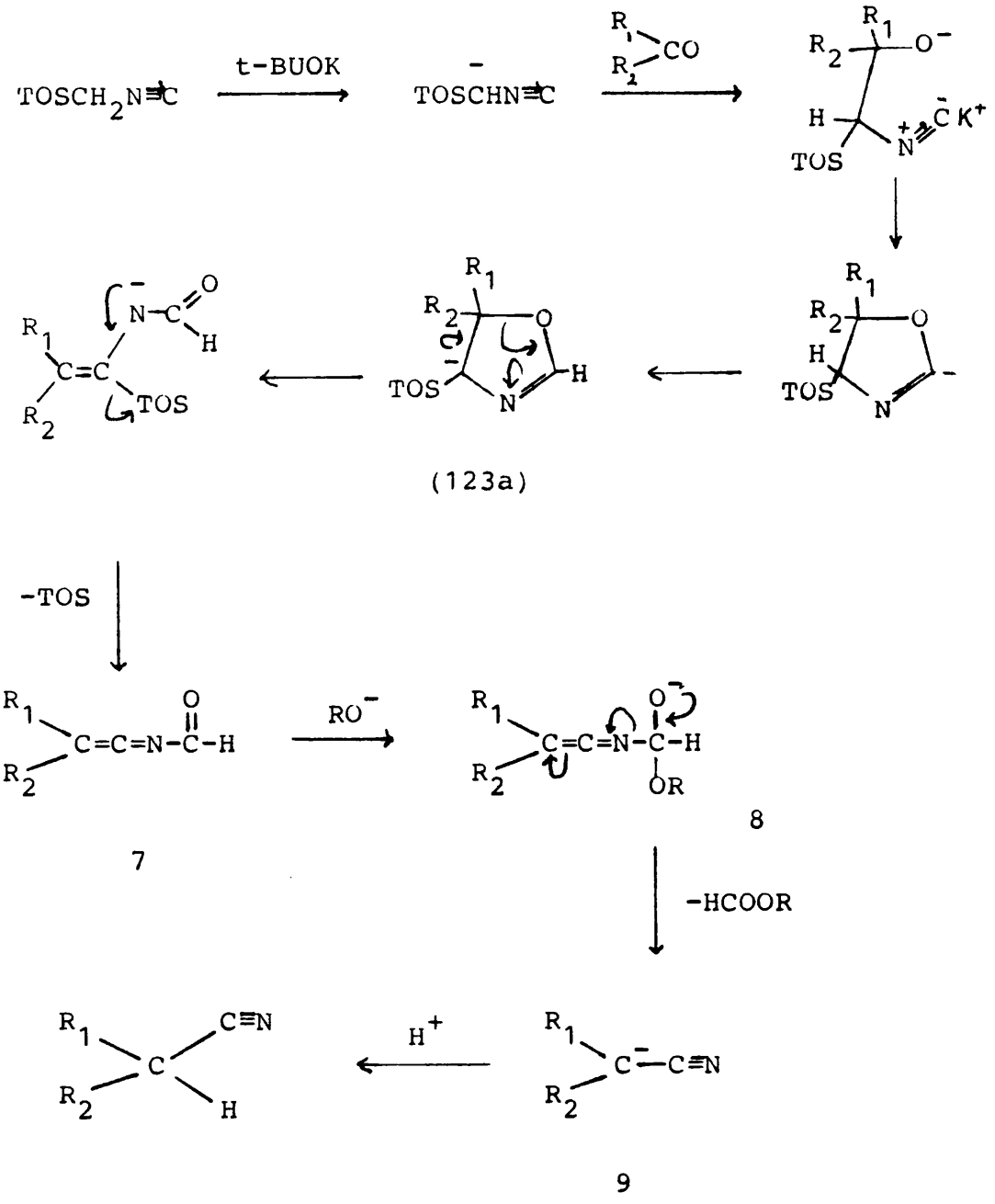
The 2,5-dimethyl-8-cyano-6,7-benzomorphan (Figure 29; 121) was prepared from the corresponding 8-oxo compound by reaction with tosylmethyl isocyanide[108] (TOSMIC,122). Potassium tertiary butoxide was added at 0°C to a solution of the 2,5-dimethyl-8-oxo-6,7-benzomorphan and 3 equivalents of TOSMIC in dimethyl sulphoxide containing some methanol. The mixture was stirred under N_2 for 1 hour at room temperature and then for 72 hours at 45°C. The reaction was accompanied by evolution of gas.



(100) (121)

Figure 29

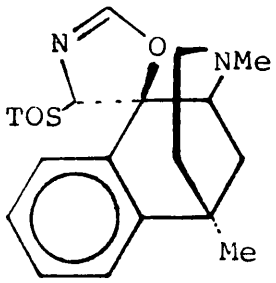
The reaction of TOSMIC is effectively a reductive cyanation, and it allows the ketone into nitrile conversion to be carried out in a single operation.[108]. This is an attractive synthetic reaction as the resulting nitrile is an intermediate which can be exploited to generate potential pharmacophores, for instance, by conversion to amine, carboxylic acid and related derivatives[128,129].



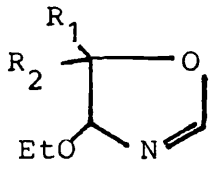
Scheme 4

The mechanism of this reaction is considered to involve a base-catalyzed condensation of TOSMIC and a ketone to give 4-tosyl-2-oxazoline[108] (Scheme 4; 123a). This intermediate has been shown to play a crucial role in the reaction, and evidence for it was obtained by the isolation of derivative (124) with sodium ethoxide in ethanol and by ^{14}C labelling experiments. The role

of the added methanol is to accelerate the final stage of the reaction, and is explained in part by its contribution to steps 7-9.



(123b)



(124)

The reaction of TOSMIC with the 8-oxobenzomorphan (100) afforded exclusively the 8α-cyanobenzomorphan (121). The large TOSMIC anion would be expected to attack the ketone from the less hindered α-side to give tosyl-substituted oxazolines (123b).

The configurational assignment for the 8-cyano compound (121) was made by ^{1}H NMR spectroscopy. Dreiding models furnished approximate dihedral angles for the C_8-C_1 segment, which assisted in relating the vicinal proton-proton coupling constant to structure. The ^{1}H NMR spectrum of the cyano compound (121) exhibits a singlet at 4.13 ppm with $JH_\beta, H_1 \simeq 2$Hz, assignable to the 8β-proton. The vicinal coupling constant corresponds by the Karplus relationship[142] to dihedral angle ($\sim 90^o$), which is consistent with that derived from Dreiding models, establishing the 8α-cyano stereochemistry. Furthermore, the bridgehead proton (H_1) is oriented in the deshielding zone of the nitrile and would be subjected to a consider-

able deshielding influence. The H_1 proton absorption occurred at a strongly deshielded position (3.42 ppm), thus confirming the stereochemical assignment.

Tosylmethyl isocyanide (TOSMIC) used in the reaction was prepared by dehydration of the N-(p-tosylsulphonylmethyl)formamide, which was derived from sodium p-toluenesulphite[130] (Figure 30). TOSMIC has also been prepared by reaction of p-tosylsulphonylfluoride with isocyanomethyllithium or by irradiation of p-tosylsulphonyl diazomethane in liquid hydrogen cyanide[131,132].

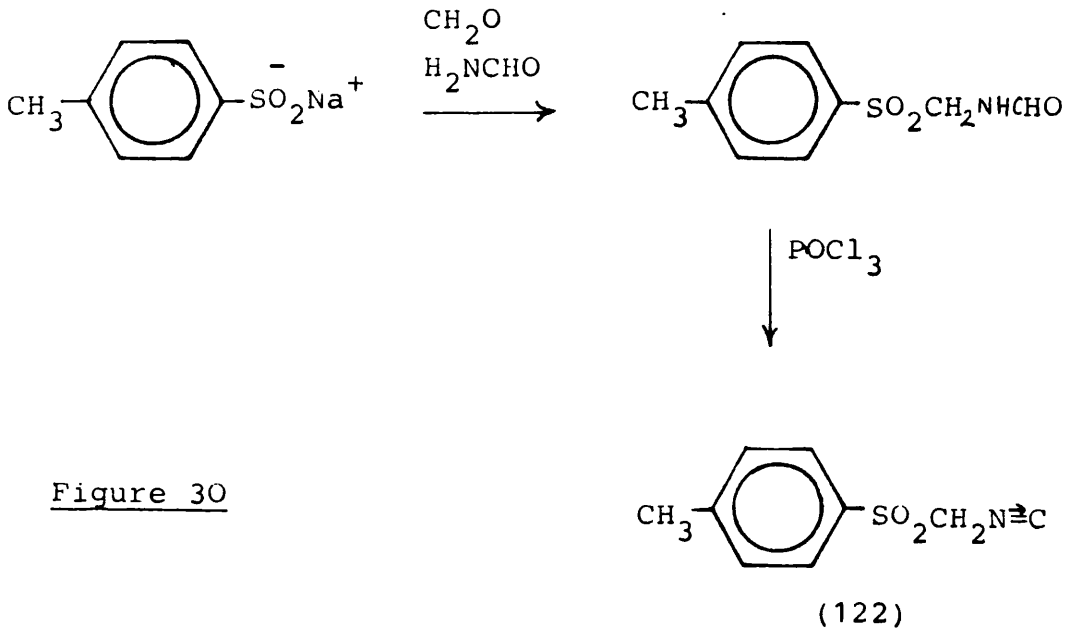


Figure 30

(122)

2.5 Attempted synthesis of 2,5,9-trimethyl-8-bromo-6,7-benzomorphan.

Bromination of the benzylic carbon of 2,5,9-trimethyl-6,7-benzomorphan, in order to offer a valuable reaction synthetic intermediate, was attempted. The most facile means of halogenation is by reactions involving free radical intermediates that effect the

homolysis of the carbon-hydrogen bond.

N-bromosuccinimide normally highly selective in attacking only activated C-H bonds, was used along with benzoyl peroxide as a radical initiator. The reaction gave a complex mixture as shown by thin layer chromatography. The PMR spectrum of the crude reaction products was more complex than anticipated and showed no indication of the presence of the required bromobenzomorphan. Attempts to separate the complex mixture, by passing the material through a silica column, and attempts to identify the components were not successful.

Examination of Dreiding models of benzomorphans illustrated that most acidic protons are sterically hindered and it is likely that bromination on other carbon atoms may occur. Under the normal conditions of reaction, N-halogenation would appear to be unimportant relative to C-halogenation; however N-bromosuccinimide is reported to effect preferential N-bromination[135]. Thus the complex mixture of products results probably from the bromination of several carbon atoms and on nitrogen. Bromination may also be complicated by possible rearrangements and/or degradation.

CHAPTER THREE

8-AMINO-6,7-BENZOMORPHANS AND THEIR DERIVATIVES

CHAPTER THREE

8-AMINO-6,7-BENZOMORPHANS AND THEIR DERIVATIVES.

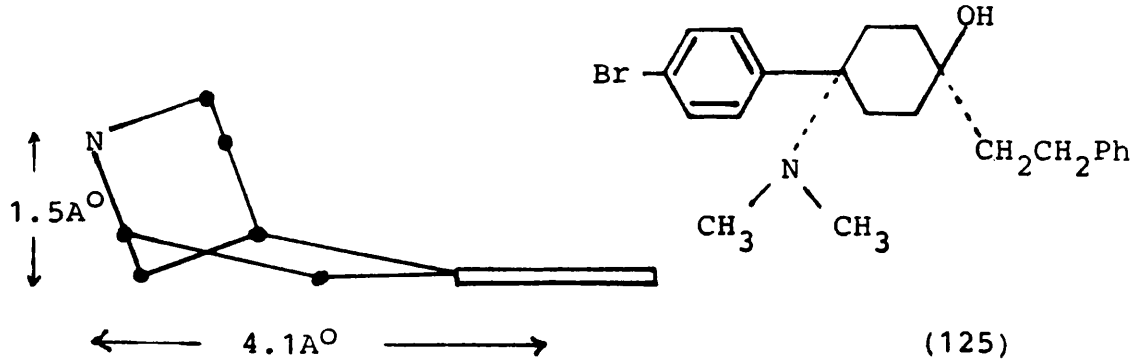
3.0 Introduction.

The mechanism by which opiates elicit their biological response is poorly understood but is known to involve principally interactions with one or more opiate receptors in the central nervous system. A necessary feature of an opiate molecule is its basic centre[10,95]. It is believed that the opiate nitrogen interacts with a receptor either *via* its lone electron pair[56,62] or in its protonated form[53-55]. In either case, the electron density on the nitrogen plays an important role in pharmacological activity.

The concept of a single receptor defined by a rigid morphine skeleton is incompatible with present-day stereochemical and structure-activity data. It is more likely that analgesics bind ionically with a relatively simple, identical anionic centre which acts as a pivot around which a variety of modes of binding may occur[64,65]. It is noteworthy that simple amines like β-phenylethylamine, 3-aminocyclohexene, 2-amino-indane fulfil the simple requirements for receptor binding in terms of structure and spacial configuration; these amines have been reported to possess some analgesic activity[136].

6,7-Benzomorphans, which are semi-rigid, afford the most versatile series of synthetic compounds for investigating the nature of opiate receptors. Chemical

modifications by altering the substituents at several positions of the benzomorphan nucleus have been intensively studied[3,24-35,61,85,106], and these modifications have led to the discovery of a considerable number of compounds possessing interesting profiles with respect to analgesic activity. Several workers have proposed that the distance of the nitrogen atom relative to the aromatic ring is critical for the interaction[137-40]. The basic nitrogen atom of the benzomorphan is rather rigidly held about 1.5A^{O} above the plane of an aromatic ring and is displaced about 4.1A^{O} from the centre of that ring (Figure 31). However, an interesting compound (125) which exhibits extremely potent opiate analgesic activity is one in which nitrogen atom is attached directly to the carbon bearing the aromatic ring[141]. It was thus of some interest to ascertain the effect on biological activity of placing a nitrogen atom at this apparently important position in the benzomorphan nucleus. In this chapter the synthesis of 8α- and 8β-amino-6,7-benzomorphan is described.



(125)

Figure 31

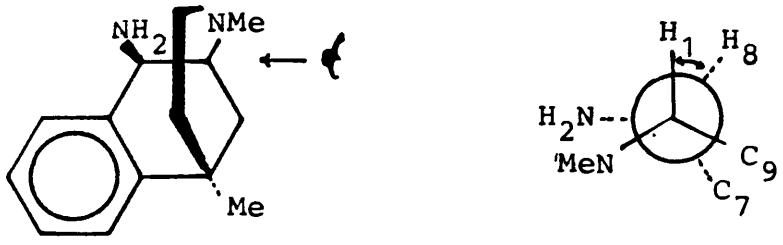
The introduction of a second nitrogen pharmacophore would affect pKa and electron density distribution of the benzomorphan, and thus should markedly influence opiate activity. It might also alter the fit between the opiate and its receptor(s), and thus may further define receptor requirements. Additionally the availability of the nitrogen non bonding electrons was modified by alkylation and acylation.

3.1 Stereoselective synthesis of the 8α- and 8β-amino-2,5-dimethyl-6,7-benzomorphan and 8α- and 8β-amino-2,5,9-trimethyl-6,7-benzomorphan.

The 8β- and 8α-amino-2,5-dimethyl-6,7-benzomorphans (126,127), key compounds in this study of amino substituted compounds, were obtained *via* reduction of the oxime (117) of 2,5-dimethyl-8-oxo-6,7-benzomorphan. Reduction of 117 with lithium aluminium hydride (LAH) gave exclusively the β-amine (126). The oxime was added to a stirred solution of LAH in diethylether under nitrogen and the mixture was stirred at room temperature overnight. Excess of hydride was destroyed with dilute aqueous sodium hydroxide and the resultant 8β-amino-6,7-benzomorphan was purified as the hydrochloride salt from ethanol-ether.

The infra-red spectrum of the product (126) shows absorption at 3475 cm^{-1} and 3400 cm^{-1} arising from stretching vibrations of two N-H bonds. Additionally the spectrum exhibits the characteristic primary amine

absorption bonds at 1603 cm^{-1} and 763 cm^{-1}. The PMR spectrum of the β-amine (126) shows the C_8 benzylic proton as a doublet at 4.05 ppm with $JH_{8\alpha},H_1 \simeq 6$ Hz. The dihedral angle between proton ($H_{8\alpha}$) and the vicinal proton (H_1) is ~30°C (Figure 32), and according to the Karplus relationship[142] $JH_{8\alpha},H_1$ would be expected to be in the order of 6.0 Hz.

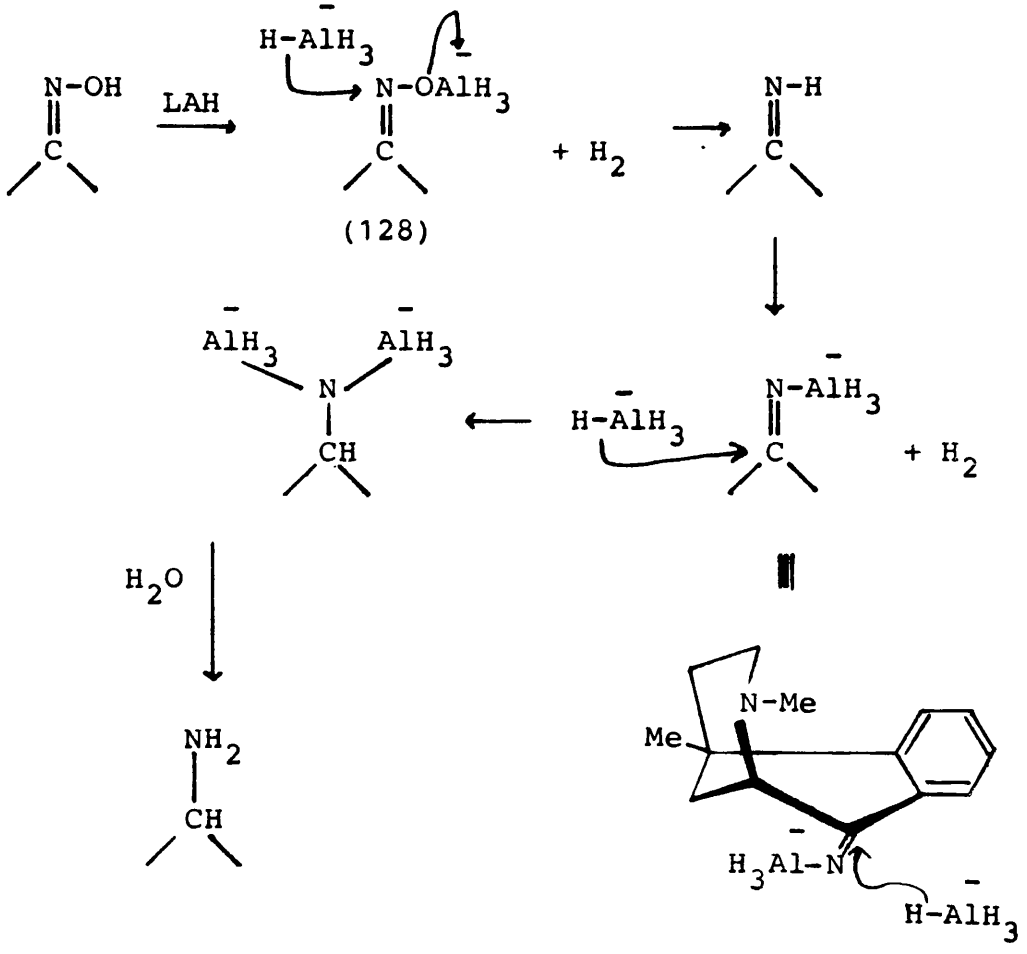


(126)

Figure 32

Lithium aluminium hydride in ether solution is postulated to exist largely as ionic aggregates of strongly solvated lithium ions and aluminohydride anions (AlH_4^-). Most reduction reactions involve the displacement of a strongly electronegative atom (oxygen, nitrogen or halogen) and the addition of a hydrogen atom to the electron deficient centre, usually a carbon atom. Hydrogen is transferred from the reactive species, the aluminohydride ion, as a hydride ion in a molecular nucleophilic displacement type mechanism. The steric course of the reduction is governed by a combination of steric interference, torsional strain and electrostatic effects in the transition state[143-145].

Theoretically, the reduction of the oxime (117) with LAH was expected to yield both α- and β-amine. However, experimentally it gave exclusively the β-amine (126). The approach of metal hydride to one side of the oxime function is clearly hindered by the iminoethane bridge between the carbon atoms C_1 and C_5. The product (126) formed is by addition of hydride ion from the less hindered α-side *viz* β-isomer.



Scheme 5

A possible mechanism for the reduction of oxime is outlined in Scheme 5. The first step is the reaction of the oxime with LAH to give intermediate (128), which

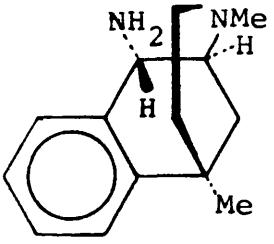
is followed by LAH attack on the nitrogen-oxygen bond as illustrated in Scheme 5[145]. The corresponding reaction of aluminium hydride, a reagent which we did not investigate, involves the addition of AlH_3 to the carbon-nitrogen double bond[146]. This electrophilic reducing agent (AlH_3) has been utilized for the reduction of oximes and is reported to give the least rearrangement products[144].

In contrast, the reduction of oxime (117) by a nickel-aluminium alloy in alkaline solution gave predominately 8α-amino-6,7-benzomorphan (127). Raney alloy was added to a stirred solution of oxime in ethanol and 2N-aqueous sodium hydroxide (1:1). No external cooling was necessary and stirring was continued for 6 hours. The resultant amine was isolated by extraction of the mixture with dichloromethane. The action of sodium hydroxide on a nickel-aluminium provides a source of hydrogen *in situ* permitting direct hydrogenation. This procedure involved, at least in part, a catalytic hydrogenation in which the hydrogen liberated is adsorbed on the surface of the newly formed Raney-nickel.

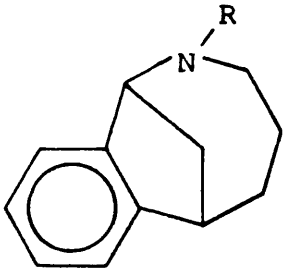
The 8α-amino-6,7-benzomorphan (127) was purified as the oxalate salt from ethanol. In contrast to the β-isomer (126), attempts to prepare a pure crystalline hydrochloride salt of α-amine (127) failed due to the hygroscopic nature. Although a single isomer was isolated, a trace of the β-isomer (127) was apparent in the PMR spectrum of the crude reaction product.

Oxalate salts have been regarded as more toxic than corresponding hydrochlorides, however, Mazzocchi et al[147] recently obtained toxicity data (mice hot plate) for the hydrochloride and oxalate salts of several β-norbenzomorphans (129) and found that, if anything, oxalates are less toxic than corresponding hydrochloride salts.

The base from a recrystallized salt of the α amino isomer (127) exhibited a proton β to the amino group with PMR absorption at 4.0 ppm as a singlet with $JH_{8\beta},H_1 \simeq 1\text{-}2Hz$. The dihedral angle between the $C_{8\beta}$-proton ($H_{8\beta}$) and the C_1 proton (H_1) is $\sim 80^{o}$ and according to the Karplus relationship[142] $JH_{8\beta},H_1$ would be expected to be in the order of 1-2 Hz.

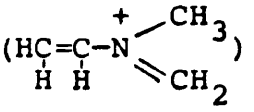


(127)

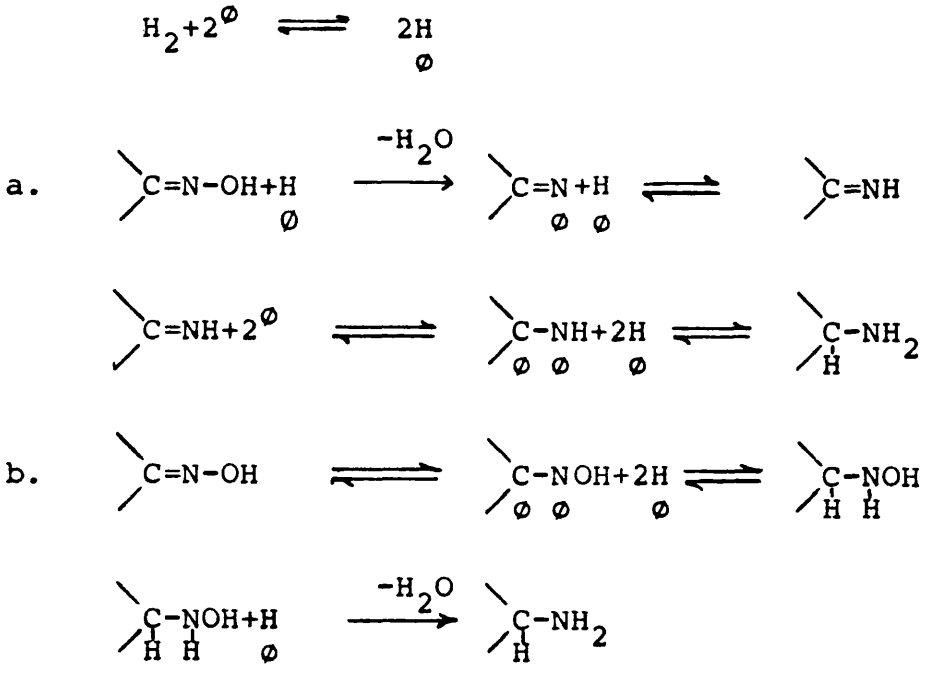


(129)

Absorption peaks at 3425 cm^{-1}, 3350 cm^{-1}, 1603 cm^{-1} and 760 cm^{-1} in the infra-red spectrum of the α-amine (127) confirmed the presence of a primary amino group. Mass spectral data gave a molecular ion at M/Z 216 corresponding to a molecular formula of $C_{14}H_{20}N_2$.

The mass spectra of the epimeric pairs of the amino-6,7-benzomorphan were indistinguishable; the base peak in each spectrum being at M/Z 70. 

The mechanism of catalytic hydrogenation is complex and remains controversial. Hydrogenation of the oxime proceeds stepwise <u>via</u> the hydroxylamine or imine. Imines are only rarely isolated as products. Hydrogenation of the oxime is considered to be similar to that of an olefin and the following Scheme 6 has been proposed in terms of the Horiuti-Polanyi mechanism[150].



ø= catalyst active site.

<u>Scheme 6</u>

The usual assumption in predicting the stereochemical outcome of catalytic hydrogenation is that the substrate will adsorb on the catalyst in such a way as to minimize steric interaction between substrate and catalyst[148-150]. The adsorption is thought to be followed by addition of hydrogen to the side of the molecule adsorbed on the catalyst[148]. This scheme does not account for the stereochemistry of the isolated α-amine (127). Hydrogenation of the oxime gives the product arising from addition of hydrogen from the more hindered side, and not as would be expected from the less hindered side.

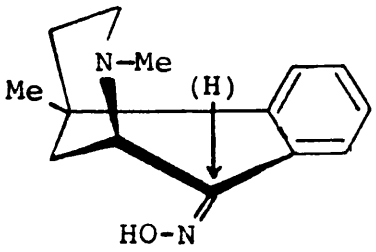


Figure 33

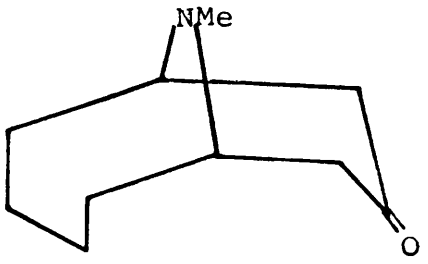
A satisfactory mechanism must explain the observed amine formed. It is reasonable to assume that the oxime group will be adsorbed preferentially so as to minimize the steric interaction between the surface and the remainder of the molecule. The hydrogen then could be considered to add from the side of molecule opposite to the catalyst, as proposed by Rideal,

resulting in the formation of the α-isomer[151](Fig. 33). According to Rideal[151] only the substrate is chemisorbed on the catalyst and that hydrogen emanates from the reaction medium. Hydrogenation proceeds with addition of hydrogen from the side of the molecule opposite to the catalyst. Farina et al[152] have obtained stereochemical evidence which lends support to the Rideal mechanism.

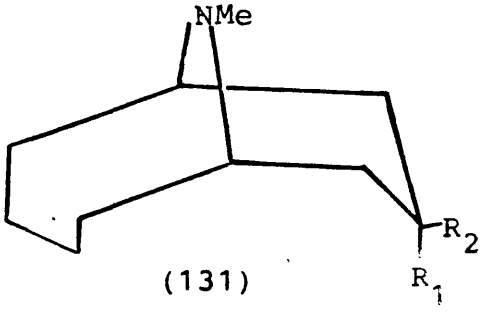
Alternatively, this result may be interpreted in terms of an interaction between the ring nitrogen atom and the catalyst surface. It is possible that the amino nitrogen may form a dative bond with the catalyst surface thus producing an anchor effect[153] which will favour the addition of hydrogen from the hindered β-face of the molecule. In general, compounds with an unshared pair of electrons on nitrogen are more readily hydrogenated in acidic rather than in basic solution. This has been ascribed to the ability of the unshared nitrogen electrons to bind with the active surface of the catalyst thus poisoning it. The amino nitrogen has been demonstrated to be capable of catalyst poisoning only when it has an unshared pair of electrons[154].

It is interesting to note that the reduction of the azabicyclodecanone (130), was reported to take place in a markedly different manner with respect to stereochemical relations[155]. In summary, catalytic hydrogenation yielded predominantly α-isomer (131a),

a result which could be attributed to the approach of the molecule to catalyst surface from the less hindered β-side. Reduction with aluminium hydride, on the other hand, gave mainly the β-isomers due to hydride transfer occuring from the unfavoured (hindered) α-face.



(130)



(131)

a. α, R_1 = OH

b. β, R_2 = OH

Similarly the stereochemistry of reduction of 9-oxo-6,7-benzomorphan (Figure 14;52) is known to be dependent on whether or not a free pair of electrons is available on nitrogen[96-99]. Catalytic hydrogenation or hydride reduction of the free base (52) affords the 9α-ol isomer (53), whereas the 9β-ol (54) is derived from the quaternary salt of (52) under similar conditions. These results may be attributed to prior complexation of the amine function with the catalyst surface or to the assistance of hydride transfer by the direct participation of the amine function. The lone pair is not available in the quaternary salt where nitrogen carries a full positive charge.

In an effort to assess the extent to which the anchor effect influences the stereochemistry of hydrogenation, reduction of the oxime (117) was carried out in an acidic media. As acid cannot be used in reductions over Raney nickel, platinum oxide was employed.

The platinum-catalyzed hydrogenation of oxime (117) in hydrochloric acid-ethanol at low pressure (3 atm.) and at room temperature gave, as a result of H_2 addition from the more hindered side, exclusively the α-amino isomer (127). The presence of acid in the reaction system apparently had no influence on product stereochemistry. This suggests that the role of the amine nitrogen in directing the course of the reduction is of minor importance and that the product determining step is hydrogen transfer to the substrate and not adsorption of the substrate on the catalyst. However, any explanation of these stereochemical results must take into account the influence which solvent and catalyst can exert upon different modes of adsorption of the oxime group onto active sites of the catalyst.

In contrast, Shiotani and Mitsuhashi[101], report the opposite stereochemical result of an oxime reduction. The oxime of 2-methyl-8-oxo-6,7-benzomorphan (Figure 21; 72) gave only 8β-acetamide (82) when reduced with platinum oxide in either acetic acid or acetic acid-sulphuric acid. However, the oxime of 2,5-dimethyl-9-oxo-6,7-benzomorphan (Figure 16; 60) was found to

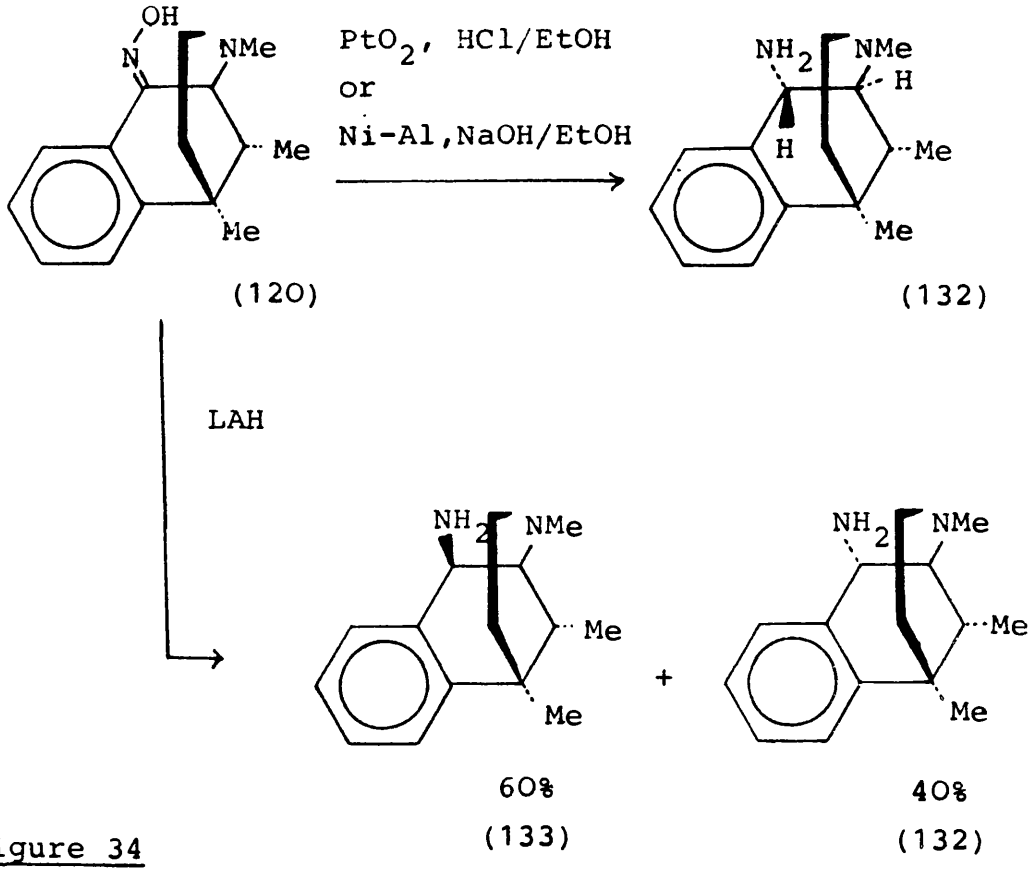
give the 9α-acetamide (62) when reduced in acetic acid-sulphuric acid and the β-isomer (63) when reduced in acetic acid alone.

3.1.1 The reduction of 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime (120) with nickel-aluminium alloy in sodium hydroxide-ethanol or with platinum oxide in hydrochloric acid-ethanol, as described for 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime (117), proceeded selectively to give the 8α-amino-2,5,9-trimethyl-6,7-benzomorphan (Figure 34; 132). The stereochemistry of the amine was determined from the PMR chemical shift and coupling constant of the C_8 proton. The $C_{8\beta}$ proton signal was observed as singlet at 3.95 ppm in $CDCl_3$ solution. The vicinal coupling constant (1-2Hz) between protons on the C_8-C_1 unit correspond by the Karplus relationship to a dihedral angle of 80°, which is consistent with that derived from the examination of Dreiding models, thus establishing the 8α amino stereochemistry.

Infra-red absorption bands indicating a primary amino group occur at 3350 cm^{-1}, 1603 cm^{-1} and 765 cm^{-1}. The structure of 132 was supported further by ^{13}C NMR, PMR and mass spectral data. The stereochemistry is consistent with that anticipated from the catalytic hydrogenation of the oxime (117) of 2,5-dimethyl-8-oxo-6,7-benzomorphan.

It is of interest to note that catalytic reduction of the 2,5,9-trimethyl-8-methylene-6,7-benzomorphan (Figure 20; 83) with Pd-C has been reported to yield

as a result of H_2 attack from the more hindered side, the 8α-methylbenzomorphan[85] (84). In contrast, the N-demethylated 8-oxo-6,7-benzomorphan (Figure 20, 85) hydrogenation under similar conditions gave the corresponding 8β-hydroxybenzomorphan [105] (86), which could be attributed to approach of the molecule to the catalyst surface from the less hindered α-side.



(120) (132)

60% (133) 40% (132)

Figure 34

In contrast to the single 8β-amino isomer obtained from LAH reduction of oxime 117, the corresponding reduction of 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime (Figure 34; 120) afforded the mixture of 8α- and 8β-amino isomers (132 & 133). ^1H and ^{13}C NMR

data obtained for the product indicated a mixture of 8α- and β-amine in a 40:60 ratio. Attempts to isolate pure β-amine (133) by fractional crystallization of the hydrochloride, hydrobromide and oxalate salts from various solvent mixtures (ethanol-ether, acetone, propan-2-ol etc.) was to no avail.

The isomeric amines (132 & 133) are readily distinguished by their PMR spectra. Protons on C_1, C_8, C_9-methyl and N-methyl are all influenced by the orientation of the amino substituent. The $C_{8\beta}$ proton signal of the α-amine (132) was observed as singlet at 3.95 ppm with $JH_{8\beta},H_1 \simeq 1$-2 Hz. The signal for the $C_{8\alpha}$ proton of the β-amine (133) appeared as a doublet at 4.02 ppm with $JH_{8\alpha},H_1 \simeq 6$ Hz. The C_9 methyl doublet in the α-amine (132) at 0.94 ppm was at slightly lower field relative to that seen in the β-amine (0.84 ppm; 133). Differences between α- and β-amines were seen also in the shifts of the N-methyl and C_1 proton signals. In the α-amine the singlet due to $N\text{-}CH_3$ appeared at 2.45 ppm, compared with 2.64 ppm for the β-amine (133). The C_1 proton signal of the α-amine (132) appeared at 2.90 ppm as an apparent doublet ($J \simeq 4$ Hz; 1-2 Hz), whereas in the β-amine the corresponding signal appeared as doublet of doublet centred at 2.70 ppm ($J \simeq 6$ Hz; 4 Hz).

The mass spectral fragmentation pattern of both 8α- and 8β-amino isomers (132 & 133) exhibited a molecular ion peak at M/Z 230, loss of an amino group

gave a radical ion peak at M/Z 213. The remaining fragmentation patterns were identical, with base peaks at M/Z 84.

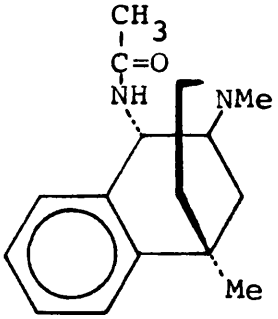
The stereochemistry of LAH reduction may be explained in terms of the steric hindrance caused by the presence of a methyl function at position 9 of 120. The approach of metal hydride to the β-side of the oxime is hindered by the iminoethano bridge between the carbon atoms C_1 and C_5. Inspection of molecular models of the oxime (120) demonstrates that a 9α-methyl group will hinder the approach of metal hydride from the more accessible α-side of the molecule, consequently there will be little difference in hindrance to attack by the reducing agent from either side of the molecule, thus leading to the formation of almost equal amounts of the epimeric amines.

Interestingly, addition of phenyl- or methyl-lithium to 2,5,9-trimethyl-8-oxo-6,7-benzomorphan has been reported to afford 8,8-difunctionalized benzomorphans (Figure 20; 80 and 82) as result of substituent addition from the α-face only[85].

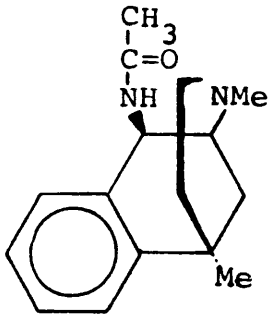
3.2 Reactions of 8-amino-6,7-benzomorphans.

3.2.1 Preparation of isomeric 8-acetamido-, 8-cyclopropionamido- and 8-phenylacetamido derivatives of 2,5-dimethyl-6,7-benzomorphan.

A primary amino function may be rendered non basic by simple conversion to an amide. Such a change could influence attack at an opiate receptor significantly. Good yields of amides (134-138) were obtained by following established procedures for acylation of amines; reacting them with the required acid chloride in the presence of base. Thus the acetamido derivatives (134,135) were prepared by the addition of the acetyl chloride in a controlled manner to the amine dissolved in dichloromethane in the presence of a mole of triethylamine. Attempts at acetylation with acetic anhydride failed and starting amine was recovered fully.

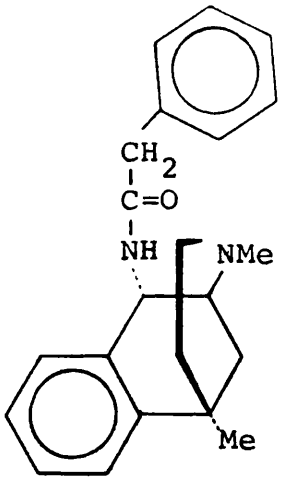


(134)



(135)

The phenylacetamido derivatives (136 & 137) were obtained by the reaction of 8α- and 8β-amino-6,7-benzomorphan, respectively, with phenylacetyl chloride in the presence of potassium carbonate in aqueous methanol. The use of aqueous methanol is effective because of its slow rate of solvolysis of phenylacetyl chloride. However, the addition of neat reagent (phenylacetyl chloride) to the amines was necessary to achieve acylation. When the reaction was attempted with phenylacetyl chloride in methanol as solvent, starting material was recovered fully. Thus no reaction had occurred, suggesting that the acid chloride may have undergone alcoholysis. Many workers, including Walters[40], have reported the preparation of phenylacetamido derivatives employing acid chloride in methanol.



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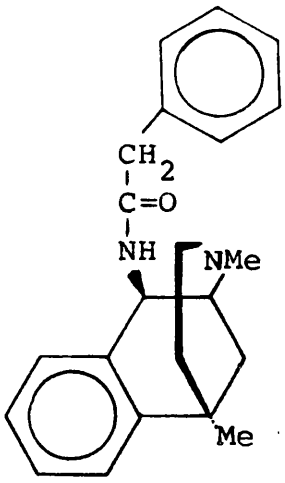


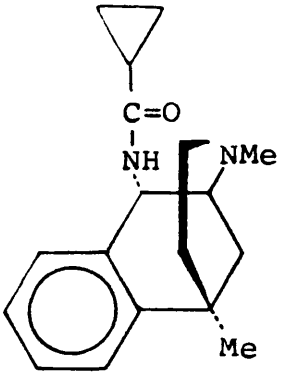
(137)

Reaction of the 8α-amine (127) with cyclopropanecarbonyl chloride in the presence of triethylamine afforded 8α-cyclopropionamido-2,5-dimethyl-6,7-benzomorphan (138) as expected. The infra-red spectrum of the product (138) exhibited typical amide absorption bands at 3295 cm^{-1} (>NH) and 1670 cm^{-1} (>CO). The PMR spectrum showed the C_8 proton doublet at 5.2 ppm with $JH_{8\beta}$,NH ≃ 10-12 Hz. Deuterium oxide exchange of the amide proton at 6.6 ppm reduced the doublet to singlet. The four protons of the cyclopropyl group appeared in the 0.6-1.1 ppm region. The molecular ion observed at M/Z 284 in the mass spectrum also supported this structure for the product (138).

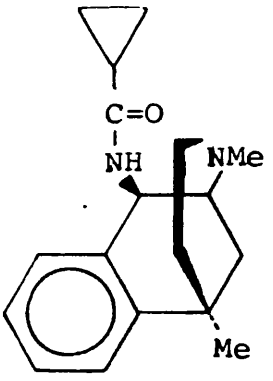
However, treatment of 8β-amine (126) with cyclopropanecarbonyl chloride in the presence of base did not give the expected 8β-cyclopropionamide but gave 8β-dicyclopropionamide derivative (140). The infra-red spectrum of the product (140) showed two strong carbonyl absorption bands at 1660 cm^{-1} and 1712 cm^{-1} and the absence of NH stretching bands.

The PMR spectrum revealed a complex pattern for the protons of the cyclopropyl group in the 0.8-1.4 ppm region, which intergrated for 8H. The C_8 benzylic proton signal was observed as doublet at 6.08 ppm instead of expected doublet of doublets at 5.2 ppm. The C_8 proton was at lower field than its normal position due to the inductive effect of an extra acyl group. The mass spectral fragmentation pattern showed a

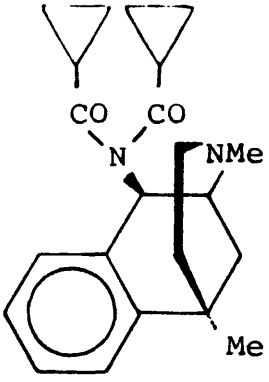
molecular ion at M/Z 352, loss of a cyclopropyl carbonyl unit gave a monoacylated radical ion at M/Z 283. The remaining fragmentation pattern was similar to that of the 8α-cyclopropionamide (138). The base peak in both compounds occurred at M/Z 70 and was ascribed to $H_2C{=}\overset{H}{\overset{|}{C}}{-}\overset{+}{N}(CH_3)=CH_2$).



(138)



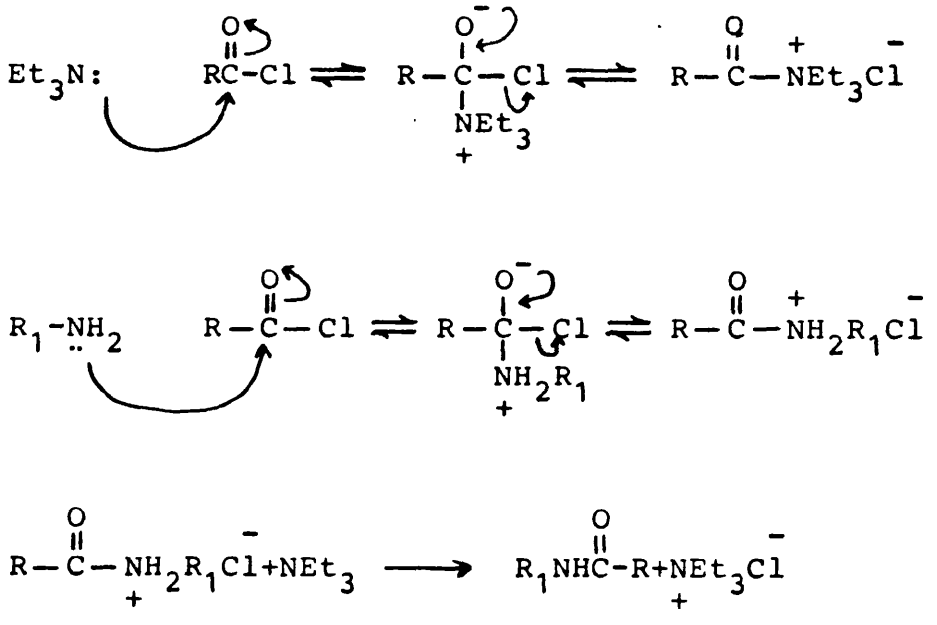
(139)



(140)

Mechanisms for acylation reactions have been proposed by several workers[158,159,160,161]. A feasible mechanism for the acylation reaction in the presence of triethylamine is shown in Scheme 7.

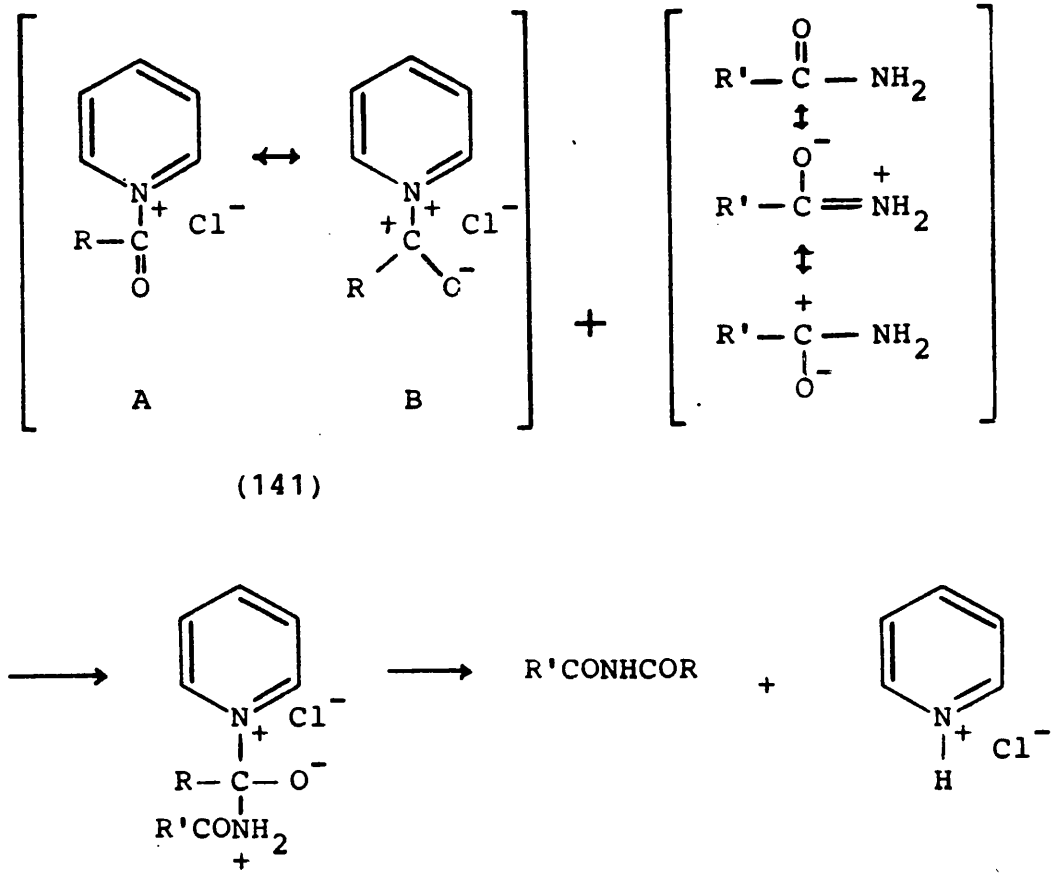
Reversible addition of the carbonyl to both amines is followed by reaction of the adduct with triethylamine. The weaker basic amine is acylated and the stronger is converted to a salt. The role of triethylamine is not only as a base to remove hydrogen chloride, but because of its ability to form a reactive intermediate with acid chloride it may possibly function as a nucleophilic catalyst. The tertiary nitrogen in the aminobenzomorphans also act as a hydrogen chloride acceptor.



Scheme 7

Acylation of a primary amine usually affords no diacyl derivative. A second acyl group is not easily introduced due to the electron drain effect of the initial acyl function at the nitrogen atom. The formation of diacylamines is possible under vigorous

conditions or in the presence of suitable basic catalyst[157]. Pyridine is resistant to C-acylation and has a great utility as a catalyst[157].



(141)

Figure 35

The addition products of pyridine and acid chlorides, the alkanoylpyridinium chlorides (Figure 35; 141), are able to acylate amides whereas the free acid chloride is ineffective. It has been suggested that this is due perhaps to a greater positivity of the acyl carbon on pyridine N in anhydrous organic solvents owing to a possible resonance contribution of the structure B, or possibly to an induction

caused by electronegative oxygen and positively charged nitrogen atom in A, which renders the acyl carbon relatively more positive and thus capable of reacting more readily with a weakly negative nitrogen centre of the almost neutral amide[157].

The relative ease of the diacyl amine (140) formation suggests that the requirements for acylation of the amide are already present in the aminobenzomorphan (126) itself, ie. the additional basic tertiary nitrogen. A possible mechanism for the diacylation of the 8β-amine (126) is outlined in Figure 36. The formation of an unstable amine adduct (142) and the intermediate (143) are thought to be involved in intra-molecular acylation. Clearly, such a transition state (143) cannot exist with 8α-cyclopropionamide or 8β-phenylacetamide, and thus the steric factors forbid the formation of diacyl derivatives.

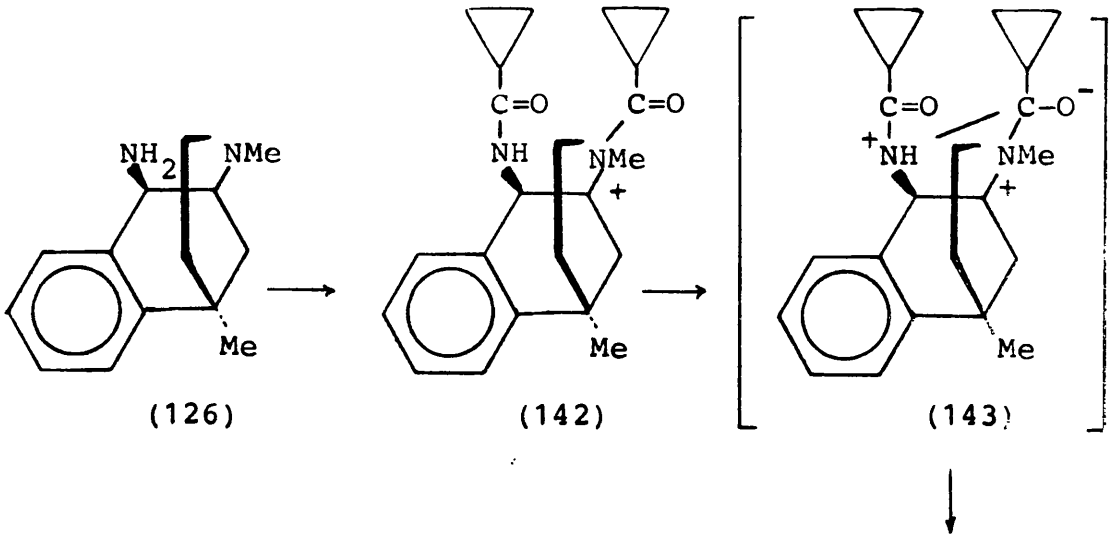


Figure 36

It was possible to prepare the desired 8β-cyclopropionamido-6,7-benzomorphan (139) in poor yields by adding exactly one equivalent acid chloride very slowly with rapid stirring to a cooled solution of the 8β-amine (126) in dichloromethane. Although the amide (139) was not obtained analytically pure, its structure was supported by IR and NMR data.

In initial attempts an excess of the acid chloride was employed as it was thought the formation of salt type adduct (144) by reaction of acid chloride with the tertiary nitrogen of benzomorphan would effectively reduce the amount of acid chloride.

$$RCOCl + R_3N \longrightarrow R_3N^+(COR)Cl^-$$

(144)

The infra-red spectrum of the amides (134-139) displayed characteristic amide carbonyl and NH stretching bands at 1640-1650 cm^{-1} and ~3295 cm^{-1} respectively. PMR spectra of the α- and β-acetamide exhibited a singlet for the acetyl methyl at 1.9 and 2.14 ppm respectively. The methylene singlet of phenylacetyl group in α- and β-phenylacetylamide (136 & 137) appeared at 3.5 and 3.69 ppm respectively. The amide proton resonated as a broad doublet at ≃ 5.9 ppm for the α-amides (134,136,138) and in the 7.0-7.2 ppm region for the β-isomers (135,137,139). In the α-isomers (134,136,138) C_8 proton appeared as a doublet at 5.2 ppm with $JH_8,NH \simeq$ 10-12 Hz which

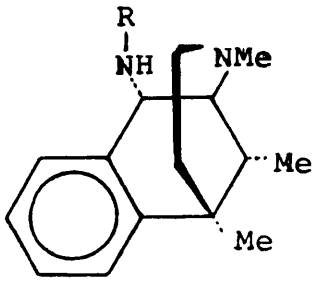
on D_2O exchange of the amide proton was reduced to singlet. The signal for the C_8 proton of the β-amides (135,137,139) appeared as a doublet of doublet centred at 5.18 ppm with $JH_8,H_1 \simeq 6$ Hz and $JH_8NH \simeq$ 10-12 Hz. D_2O exchange of the amide proton changed the multiplicity of this absorption to the expected doublet. ^{13}C NMR and mass spectral data were consistent with the assigned structures of the amides.

3.2.2 Preparation of 8α-acetamido-, 8α-cyclopropionamido- and 8α-phenylacetamido-2,5,9-trimethyl-6,7-benzomorphan.

The title compounds (145-147) were prepared from 8α-amino-2,5,9-trimethyl-6,7-benzomorphan (132) essentially in the same manner as that described earlier (section 3.2.1) for 8-amino-2,5-dimethyl-6,7-benzomorphans, namely by reacting the amine with the required acid chloride in the presence of base.

These amides (145-147) were identified by their NMR, mass and infra-red spectra. Infra-red spectra exhibited typical amide stretching absorption bands between 3400-3200 cm^{-1} and 1630-1670 cm^{-1}. The C_8 proton signal of the amides (145-147) was observed as a doublet at 5.24 ppm with $JH_{8\beta},NH$=10-12 Hz which on deuteration with D_2O collapses to the singlet. The signal for the amide proton was found as a doublet in the 5.5-5.8 ppm region. Other PMR absorptions for the

amides and mass spectra were consistent with the assigned structures (145-147).



145. R = $COCH_3$

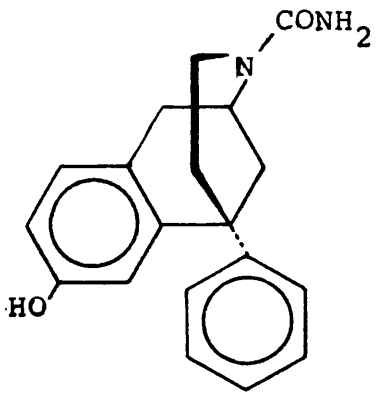
146. R = CO– 

147. R = CO–CH_2– 

Most narcotic analgesics bear a nitrogen functionality of sufficient basicity to be predominantly protonated at physiological pH, and the electron density about nitrogen is important in opiate activity. The introduction of an acyl substituent on the 8-amino group would change the electron density distribution throughout the molecule and affect the pKa of the drug. It may also distort the molecule and the distortions could cause a change in the fit between opiate and its receptor. Further, the acyl group may directly participate in binding to the receptor and thus may further define receptor requirements.

The importance of nitrogen basicity for pharmacological activity has been studied and it is reported

that reduced basicity results in a loss of activity[162]. This loss was ascribed to inefficient transport to relevant receptor sites of compounds resistant to protonation at the physiological pH. It is surprising that the N-carboxamide[67] (148) which lacks a basic centre is reported to be an orally effective analgesic.



(148)

3.2.3 Synthesis of 8α- and 8β-(ethylamino)-2,5-dimethyl-6,7-benzomorphan, 8α- and 8β-(cyclopropylmethylamino)-2,5-dimethyl-6,7-benzomorphan, and 8α- and 8β-(phenylethylamino)-2,5-dimethyl-6,7-benzomorphan.

The nitrogen substituents of the opiates play a complex role in effecting pharmacological responses, which range from potent agonism through mixed agonism-antagonism to pure potent antagonism[3,26,61,93]. Other structural modifications such as an axial C_{14}-OH group on the morphine, C_9-OH group in the benzomorphans and long chain tertiary carbinol substituents on C_7 in the

oripavine series, effect the relative analgesic agonist-antagonist potencies for any given N-substituent.

In the 6,7-benzomorphan series (eg. metazocine; 14) replacement of N-methyl by saturated alkyl moieties from ethyl to butyl causes reduction or loss of analgesic activity and concurrent gain in narcotic antagonist activity[81,93]. When a five or six carbon side chain is introduced to form N-pentyl or N-hexyl compounds, the potent analgesia associated with the parent N-methyl compound is restored. An N-phenylethyl group gives a particularly enhanced analgesic activity, and phenazocine (17; R = CH_2CH_2ph) is in clinical use. A similar replacement of N-methyl by N-phenylethyl groups in non-phenolic benzomorphans may actually reduce activity.

A similar variation of analgesic potency is observed in homologous normorphine and morphinan series. Maximal analgesic potency is noted with N-methyl and N-pentyl, and a loss of analgesic potency occurs with N-ethyl and N-butyl derivatives[3,5].

6,7-Benzomorphans unsubstituted on the nitrogen atom generally do not display antagonist behaviour in primates but have been shown to have a weak antagonist component by their action on the guinea pig ileum[163]. Conversion to partial antagonists has been effected by replacing N-methyl with allyl, propyl and cyclopropylmethyl. Many mixed agonist /antagonists prepared in this manner are potent and some find clinical

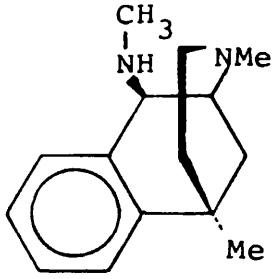
applications. Pentazocine (17; R = CH_2-CH = CMe_2), an analgesic with antagonist activity, is firmly established as an analgesic of value in a reasonably wide range of pain situations[4,27].

However, antagonist activity is not limited to the above substituents or to tertiary amines; more recently even N-methyl compounds have been reported to possess antagonist properties[31,35]. It is suggested that the only required structural feature for the production of antagonist activity is a certain degree of nitrogen crowding, above or below which agonist activity prevails. An alkyl substituent at a centre remote from the nitrogen is also known to change drastically the ratio of agonist to antagonist activity[12,164].

Reductive alkamination of 8-oxobenzomorphan (100) presents a synthetic route to 8-alkylamino-6,7-benzomorphans required for pharmacological evaluation in this project. Work by Borch et al[165] demonstrated the feasibility of employing the cyanohydridoborate anion (BH_3CN^-) as a selective reducing agent in a reductive amination. Reaction of 2,5-dimethyl-8-oxo-6,7-benzomorphan (100) with anhydrous methylamine in HCl-methanol in the presence of sodium cyanohydridoborate furnished the corresponding 8β-methylamino-6,7-benzomorphan (149) in poor yields, with the 8β-hydroxy-6,7-benzomorphan (150) as a by-product. Separation of these products was achieved by passing the crude

material through a silica column, and they were characterised by their infra-red and NMR spectra.

Attempts to minimise undesired side reactions and to improve yields of the amine (149) by modifying reaction conditions met with only limited success. Usually the reduction of ketones to alcohols with sodium cyanohydridoborate is much slower than reductive amination. Reduction of the imminium group ($\backslash C=\overset{+}{N}HR$) with cyanohydridoborate anion is rapid at around pH 6 but that of ketone is negligible[165].



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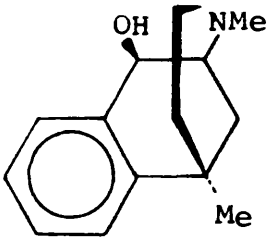


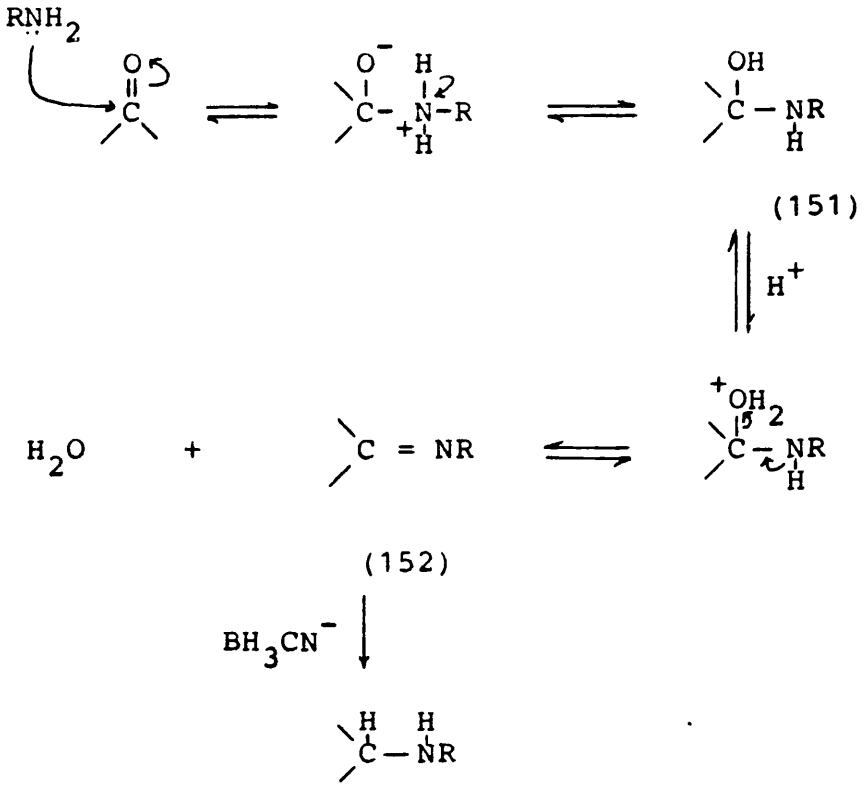
(150)

The stereochemistry of these compounds was assigned from their NMR spectra. The benzylic C_8 proton in the PMR spectrum of 8β-methylamine appears as a doublet (J=6 Hz) at 3.65 ppm. The coupling constant is identical of that of the 8β-amino-6,7-benzomorphan (126) and by analogy indicates that it is the 8β-isomer. The signals of the 8-NH proton and 8-N-methyl protons were seen as singlets at 2.05 ppm and 2.60 ppm respectively. In the spectrum

of 8β-hydroxybenzomorphan (150) the C_8 proton appears in a downfield position at 4.70 ppm also as a doublet (J=6 Hz). The hydroxyl proton resonates as a broad singlet centred at 3.90 ppm.

Interestingly, the addition of hydrogen to both the imine and carbonyl groups is stereospecific; hydride transfer from sodium cyanohydridoborate occurring from the more accessible α-face leading to the 8β-OH and NH-R isomers. This is consistent also with known methyl- and phenyl lithium additions of 8-oxobenzomorphans (79) or LAH reduction of oxime (117) which gave exclusively 8β-isomer (126). Catalytic reduction of oxime (117) gave the 8α-aminobenzomorphan (127), and hydrogenation of the imine under similar conditions may be expected to yield 8α-alkylamino-6,7-benzomorphan.

The first steps in a reductive alkamination involve substitution on nitrogen by the activated carbonyl compound to form a carbinolamine (151) which is followed by dehydration to give imine (Scheme 8;152). Imine formation is an equlibrium process and the removal of water produced is advantageous. The rate-determining step of the reaction is pH dependent. In neutral solution the rate-determining step is the dehydration of the carbinolamine intermediate. However, at low pH the dehydration becomes fast, and as result of the decrease in concentration of free amine, the attack of amine upon carbonyl becomes rate-limiting.



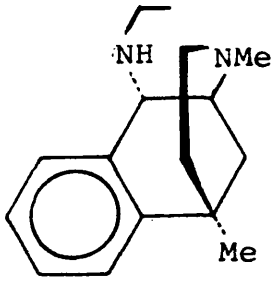
Scheme 8

Reductive alkylation is dependent to a large extent upon the reactivity of the carbonyl function. It is well known that conjugated carbonyl compounds are less reactive with usual carbonyl reagents than are the saturated analogues, presumably because of the greater electron density at the carbonyl carbon in the former case. Hindered ketones eg. pinacolone are reported not to react with amine[165]. Examination of a Dreiding model of 8-oxobenzomorphan (100) showed the 8 position to be sterically hindered. Since the 8-oxo-6,7-benzomorphan (100) itself is reduced with BH_3CN^-, the poor yield of 8β-methylamino-6,7-benzomorphan may be due to difficulty of the imine formation step. It was clear that difficulty of imine formation with bulky amines (eg. phenylethylamine) will be even more

acute, and consequently this synthetic route was abandoned in favour of the usual procedures[93,168].

A fairly representative group of 8-alkylamino-2,5-dimethyl-6,7-benzomorphans (153-158) was prepared following the established literature procedure for the acylation of amine and the subsequent reduction of the resultant amide. Thus 8β- and 8α-amino-6,7-benzomorphans (126 & 127) were treated with the appropiate acid chloride in the presence of a hydrogen acceptor to afford amides, as described in section 3.2.1. The intermediate amides were reduced with LAH in ether or tetrahydrofuran (THF) to yield the corresponding N-alkylated amino-6,7-benzomorphans (153-158) in fair to poor yields. That reduction had occurred was indicated by loss of a PMR signal for the amide proton and the absence of a carbonyl stretching band in the infra-red.

Lithium aluminium hydride reduction of 8-phenylacetamido derivatives (136,137) required drastic conditions which included heating in refluxing THF solution (65^{o}) and a longer reaction time. These reaction conditions resulted in poor yields of the 8-phenylethylamino-6,7-benzomorphans. It would appear that harsh conditions lead to decomposition of the amide and/or the amine formed. The slow rate of reaction observed for the phenylacetamido derivatives and especially for the β-isomer (158) was attributed to more stringent steric requirements and to the low solubility of these intermediates.



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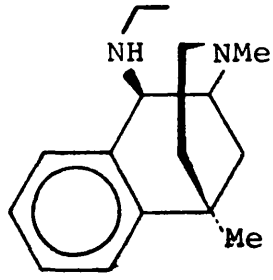

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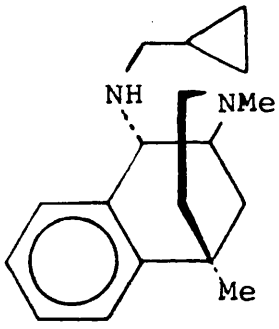

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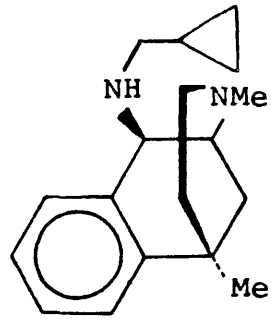

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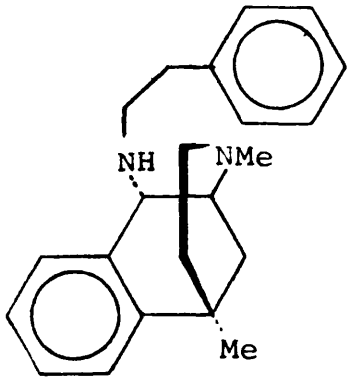

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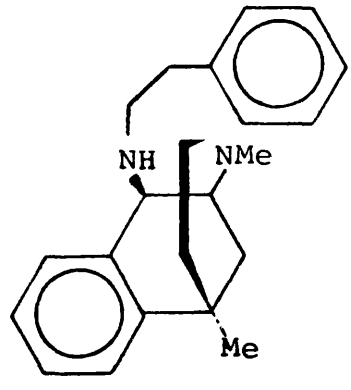


(158)

Reduction of 8β-dicyclopropionamido-6,7-benzomorphan (140) with LAH did not give 8β-dicyclopropylmethylamine but gave 8β-cyclopropylmethylamino-6,7-benzomorphan (156) identified by IR, PMR, ^{13}C NMR and mass spectral data.

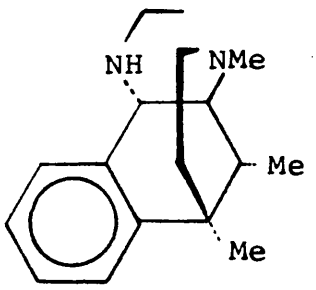
The relative instability of amides to both basic and acidic conditions is well known. LAH is a very strong base in addition to being a powerful reducing agent. It may be that reduction of the diacylated compound (140) with basic LAH results in cleavage of one acyl fragment to form the 8β-cyclopropionamide (139), which is subsequently reduced to the 8β-cyclopropylmethylamino-6,7-benzomorphan (156). A possible mechanism would involve the nucleophilic displacement of the acyl fragment by aluminohydride.

NMR, infra-red and mass spectra were consistent with the assigned structures of the alkylamines. Infra-red spectra exhibited a typical amine stretching absorption band at 3340 cm^{-1}. PMR spectra of 8α- and 8β-ethylamino derivatives (153 & 154) exhibited a triplet at ≃1.2 ppm (J= 8-10 Hz) for the methyl of ethylamino group. Chemical shifts for these protons are influenced by the stereochemistry of the amino substituent; the signals of the β-isomer (154) was at lower field relative to the α-isomer (153). The spectra of 8α- and 8β-cyclopropylmethylamino-6,7-benzomorphans (155 & 156) exhibited a broad multiplet in the 0-1.2 ppm region for the cyclopropyl group. A doublet at 2.68 ppm (J≃4 Hz) was assigned to the methylene α to the cyclopropyl group. The signal of the methylenes α and β to the 2^{o} amino nitrogen in the 8-phenylethylamino derivatives (157 & 158) were present as complex multiplet at ≃3.0 ppm.

The stereochemical assignments for the isomeric amines has been deduced previously on the basis of NMR evidence (section 3.2). The C_8 proton signal of the α- and β-alkylamines were observed as a singlet and as a doublet (J≃6 Hz) at ≃3.8 ppm, respectively. The coupling constants between the C_8 proton and the C_1 proton were identical to those of their precursors.

3.2.4 Synthesis of 8α-ethylamino-2,5,9-trimethyl-6,7-benzomorphan and 8α-cyclopropylmethyl-amino-2,5,9-trimethyl-6,7-benzomorphan.

The target compounds (159 & 160) were synthesized from 8α-amino-2,5,9-trimethyl-6,7-benzomorphan by direct acylation of the amine followed by LAH reduction of the amide intermediate, in the same manner as that described for the 8-amino-2,5-dimethyl-6,7-benzomorphan.



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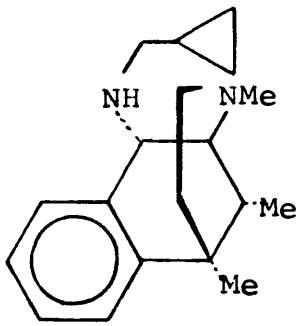


(160)

PMR,IR and mass spectral data for 8α-ethylamino- and 8α-cyclopropylmethylamino-6,7-benzomorphan were consistent with the structure assignments (see experimental part). They were purified as hydrochloride salts from ethanol.

CHAPTER FOUR

SOME POTENTIAL LONG ACTING NARCOTIC ANALGESICS AND A NEW BRIDGED AMINOBENZOMORPHAN

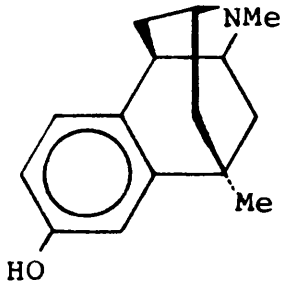
CHAPTER FOUR

Some potential long acting narcotic analgesic and a new bridged aminobenzomorphan.

4.0 Introduction.

The structure-activity effects of altering the substituents at several positions of 6,7-benzomorphan have been intensively studied, and these modifications have produced many compounds possessing interesting profiles with respect to narcotic antagonist and analgesic activity[3,24-35,61,85-106]. The benzomorphan skeleton itself has been modified and its effect on activity determined[78]. Analgesic activity has been found in a number of homologues of 6,7-benzomorphan including the B-nor, C-nor and C-homobenzomorphan[78, 106,140,169]. May and his co-workers[170] have prepared 6,7-benzomorphan derivatives where the methano bridge of benzomorphan has been omitted in order to determine the role of the methano bridge for analgesic activity. Cavestri and Mokotoff[171] have synthesized 2-azabicyclo (3.3.1) nonene derivatives, in order to test the necessity of the aromatic ring for analgesic activity; no significant activity was found for these compounds. Recently, Montzka and Matiskella[172] have introduced a methylene group to connect the 3 and 8 positions of a 6,7-benzomorphan (161). This modification gave compounds with interesting narcotic antagonist and analgesic activity. Synthesis of other bridged benzomorphan derivatives and their analgesic properties have been reported[106,173,174].

In order to investigate further the structure-activity relationships in the benzomorphan series, we decided to introduce another bridging group connecting the ring nitrogen and the benzylic carbon, C_8, via an amino group (165). This modification creates a rigid bridged tetracyclic ring system and should affect the steric environment about the ring nitrogen and above the aromatic ring. Several workers have proposed that this steric environment may be important for binding at the receptor site[54-56,176].



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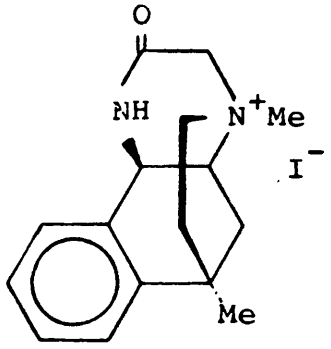


(165)

In this chapter, the syntheses of 8-chloroacetamido-6,7-benzomorphans (162 & 163), 8-chloroacetamidomethyl-6,7-benzomorphan (164) and 2,8-bridged benzomorphan derivative (165) are described. 8-Chloroacetamido derivatives are potential long acting narcotic analgesics, which may be employed as receptor labels.

4.1 Synthesis of 8α- and 8β-chloroacetamido-2,5-dimethyl-6,7-benzomorphan and 8α-chloroacetamidomethyl-2,5-dimethyl-6,7-benzomorphan.

These compounds were prepared by reacting the appropriate amine with chloroacetyl chloride in presence of triethylamine, under an atmosphere of nitrogen. Chloroacetyl chloride and triethylamine were freshly distilled prior to use. The neat acid chloride was added very slowly with a microlitre syringe to a cold stirred solution of amine in a dry acetone.

Treatment of 8β-amine (126) with chloroacetyl chloride gave a mixture which proved difficult to separate. PMR and IR spectra of the product indicated that the mixture contained the desired 8β-chloroacetamide (162). Thin layer chromatographic investigation on the product obtained after work-up demonstrated a mixture of two major components of very different Rf value. The more mobile component was identified as 8β-chloroacetamide by comparison with an authentic sample. Several attempts to isolate a pure sample of 8β-chloroacetamide (162) by crystallization of the hydrochloride or oxalate salt from various solvent mixtures, gave only a small amount of impure material. It was observed that excessive heating during crystallization or work up led rather easily to some further changes of the 8β-chloroacetamide compound, partly into a polar substance (TLC) of unknown character. Attempted isolation of 8β-chloroacetamide by column

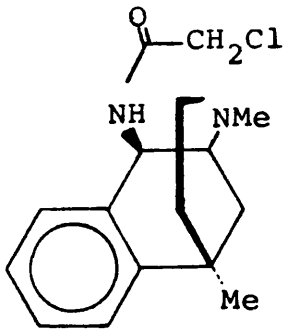
chromatography on silica gel eluting with varying strengths of methanol/dichloromethane (1-10%) caused a chemical alteration in the nature of the reactive chloroacetamide.

It became clear subsequently that the desired 8β-chloroacetamide derivative formed, underwent further reaction in presence of triethylamine in course of isolation to yield the intractable product. To circumvent this reaction, the triethylamine hydrochloride precipitate was removed by filtration from the reaction mixture prior to work up. Work up gave a crude 8β-chloroacetamide which was converted into the hydrochloride salt and crystallized from ethanol-ether to give pure 162.

8α-Chloroacetamido-6,7-benzomorphan (163) and the 8α-chloroacetamidomethyl-6,7-benzomorphan (164) were prepared by a similar procedure from the corresponding 8α-amino-6,7-benzomorphan (115) and 8α-aminomethyl-6,7-benzomorphan (184; see chapter 5), respectively. It was necessary to separate the triethylamine hydrochloride prior to work up, to ensure that only the chloroacetamido derivatives were isolated. 8α-Chloroacetamido-6,7-benzomorphan (163) was purified as its base by crystallisation from ethyl acetate. The 8α-chloroacetamidomethyl derivative (164) was converted into its hydrochloride salt and crystallized from ethanol-ether.

The spectral characteristics of both chloroacetamides were in accordance with the assigned structures. The infra-red spectra has a carbonyl absorption at 1670 cm^{-1} and an amide NH band at 3330 cm^{-1}. The PMR spectra of the 8α- and 8β-chloroacetamido derivatives (162 & 163) show several interesting features. The amide proton of the β-isomer is at lower field (8.0 ppm) compared with that of α-isomer (6.6 ppm) presumably due to the anisotropic effect of the aromatic ring. The methylene singlet of the chloroacetamide group in β-isomer (162) also appeared at slightly lower field (4.18 ppm) compared to that of the α-isomer (4.0 ppm). The C_8 proton in α- and β-isomers (162 & 163) appeared as a doublet (J≈6 Hz) and doublet of doublets (J≈6 Hz; 10-12 Hz) respectively. These couplings are consistent with the C_8 proton in the α-isomer (163) being coupled to the N-H and the β-isomer (162) being coupled to both the N-H and the proton at C_1.

The assigned structure of 8α-chloroacetamidomethyl-6,7-benzomorphan (164) is also consistent with its PMR data. The signal for the amide proton was found as a broad singlet centred at 6.8 ppm. The methylene signal of the chloroacetyl function was observed as a singlet at 4.07 ppm. The complex multiplet in the 3.0-3.80 ppm region (3H) was assigned to the C_8 proton and the methylene α to the amide nitrogen.



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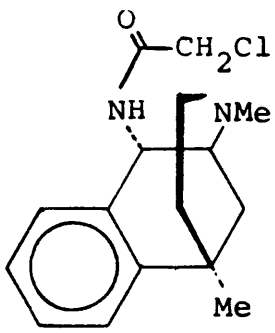

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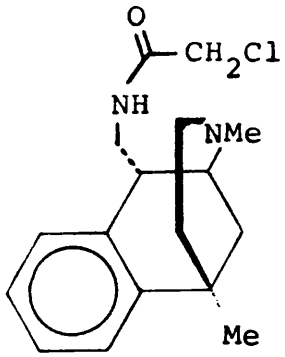


(164)

Mass spectra of both the α- and β-chloroacetamido derivatives (162 & 163) exhibited a molecular ion at M/Z 292 and fragmentation patterns gave eight major fragment ions above M/Z 50 with intensity greater than 20% of that of the base peak. The fragmentation patterns of both isomers were very similar. The possible fragmentation of the molecular ion are illustrated in Figure 37. Interpretation of the spectra is based upon the assumption that upon electron impact one electron is removed either from the nitrogen atom (166) or from the aromatic nucleus (169). Some localization of charge on nitrogen in the molecular ion is expected to be followed by preferential cleavage of the carbon$_1$-carbon$_8$ bond β to the nitrogen to form radical ion (Figure 37; 167), and the fragmentations to all the major peaks can be ascribed to that ion. Ions at M/Z 277 and 256 are due to loss of C_5 methyl and chlorine respectively. The ion of

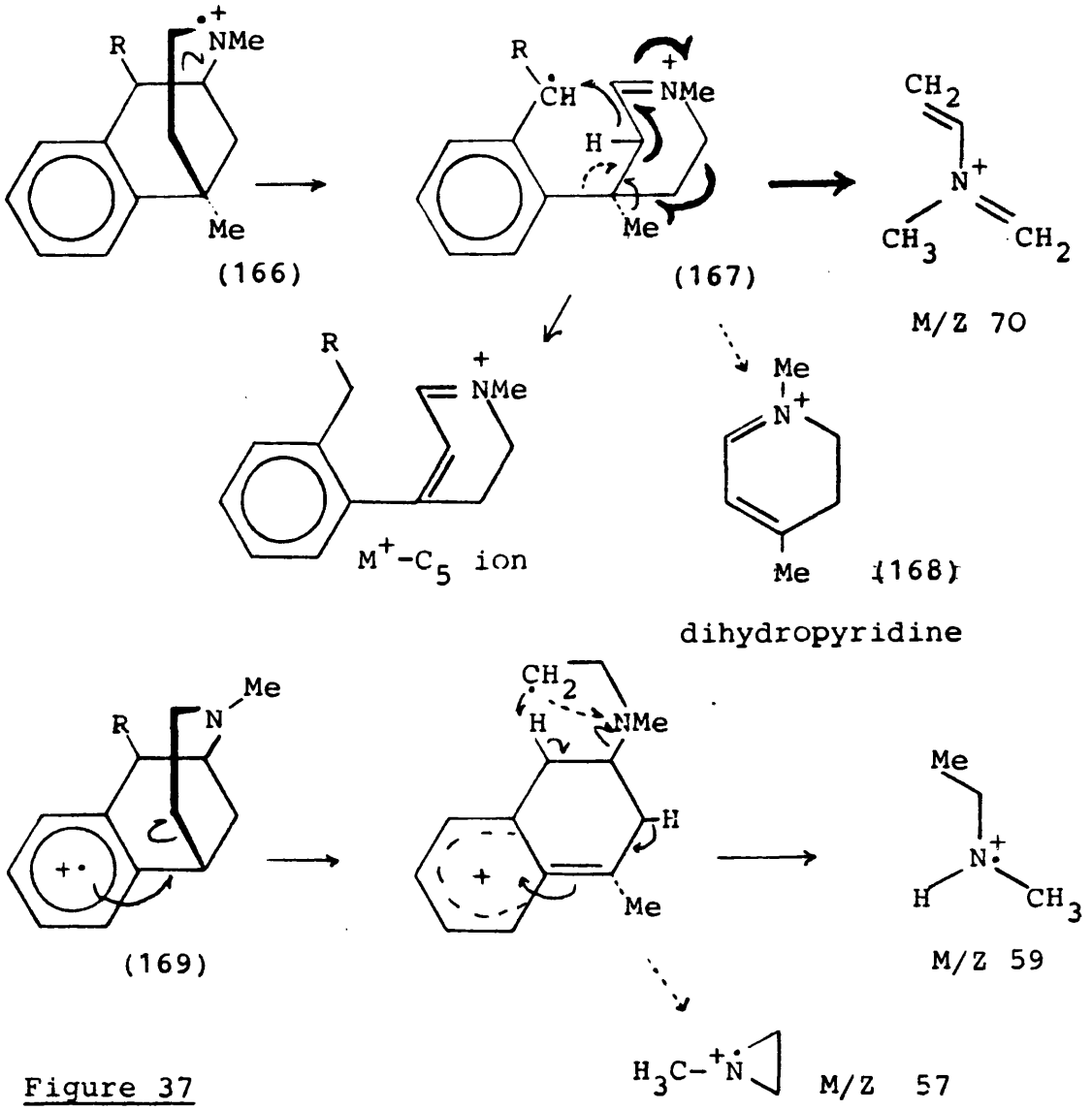
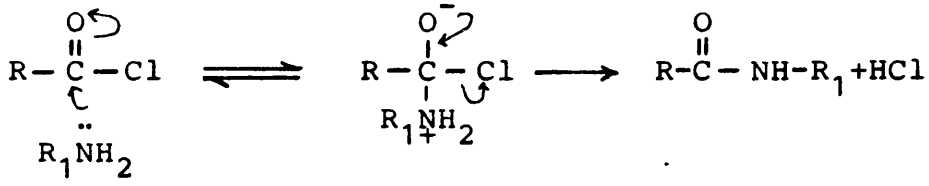


Figure 37

M/Z 199 arises from the loss of the chloroacetyl unit and C_5 methyl. The less intense ion (35% abundance) at M/Z 184 is derived from the loss of the C_5-methyl and the chloroacetylamido group. At M/Z 110 (90% abundance) is a line attributed to the dihydropyridine ion (168). This ion may be formed by migration of a hydrogen from C_9 to C_8, followed by the loss of the aromatic moiety as depicted in Figure 37. A retro Diels-Alder fragmentation of M^+ gave rise to the base peak at M/Z 70. Ions of M/Z 59 (C_3H_9N) and 57 (C_3H_7N) are presumably due to nitrogen containing bridge with or without

additional hydrogen atoms[176-180] (Figure 37).

The mass spectral fragmentation pattern of 8α-(chloroacetamidomethyl)-6,7-benzomorphan showed M^+ at M/Z 306. Loss of the C_5-methyl from M^+ afforded a radical ion at M/Z 291 (85% abundance). The dihydropyridine ion at M/Z 110 constitutes the base peak.



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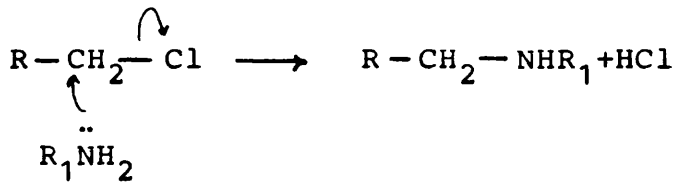


Scheme 9

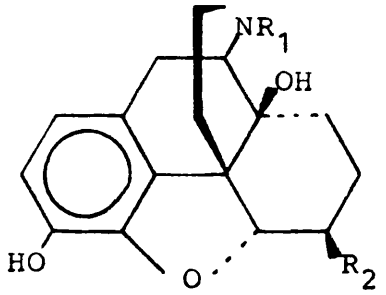
Acyl halides are in general more reactive towards 1^o and 2^o amines than are alkyl halides and the products of the reaction of 8-amino-6,7-benzomorphan with chloroacetyl chloride are as expected. The reaction of an acyl halide with a nucleophile differs from the SN_2 reaction of an alkyl halide in that the former gives a discrete intermediate, whereas the latter does not (Scheme 9). The factors governing the ease of reaction are essentially the same in the two types of reaction. The acyl halide reaction involves the formation of a tetrahedral intermediate by addition

of amine across the carbonyl double bond in an equilibrium step which then decomposes to products.

Compounds 162-164 possess a reactive halide and thus have the potential for alkylating nucleophilic centres such as SH,SMe,NH_2,OH on or near receptors with which the principal pharmacophores interact. They may therefore be useful as long acting pharmacological probes, also revealing valuable information on the location of nucleophilic sites on the receptor.

Radiolabelled opiates are used extensively as pharmacological tools for the investigation of narcotic receptors but their reversible interactions sets a limit to their value. Groups capable of forming covalent bonds at opiate receptor sites, therefore, would prove to be of considerable value as pharmacological probes. The strict structural features necessary to maintain opiate activity markedly limit the location and size of potential reactive substituents. There have been a number of attempts[181-187] to develop such agents; and the first two receptor site-directed alkylating agents (170a & 170b, R_2=$N(CH_2CH_2Cl)_2$) that are effective both in *vitro* and in *vivo* have been reported only recently. These ligands are derivatives of **β**-naltrexamine (170a, R_2=NH_2) and **β**-oxymorphamine (170b, R_2=NH_2) in which an alkylating function is attached to the 6**β**-amino group[185]. Subsequently, different long acting hydrazone derivatives (Figure 38,171) of naloxone, oxymorphone and naltrexone have

also been described[187]. The mechanism through which these hydrazone derivatives produce their long acting effect in vivo and in vitro is not known. There is no conclusive evidence of covalent linkage between hydrazone drugs and opiate binding sites.



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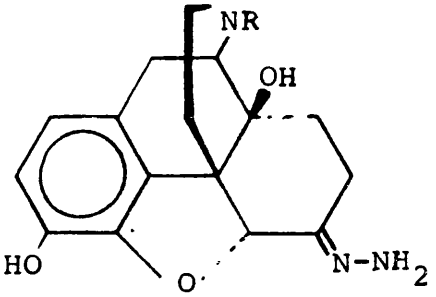


(171)

a. $R_1 = CH_2\text{-}c\text{-}C_3H_5$ Naloxazone $R = -CH_2\text{-}CH{=}CH_2$

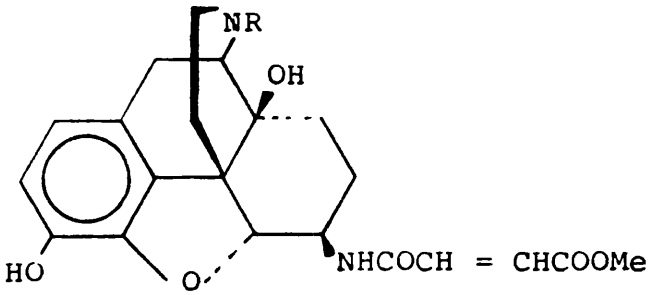
b. $R_1 = CH_3$ Oxymorphazone $R = CH_3$

Naltrexazone $R = -CH_2\text{-}c\text{-}C_3H_3$

Figure 38

Portoghese et al have recently used the derivatives of oxymorphone and naltrexone containing an identical alkylating moiety (172a & 172b) and have provided support for the multiple modality receptor concept[186]. Only the N-cyclopropyl compound (172b) was found to bind covalently to opiate receptors although both compounds form a receptor complex. This suggests that either they interact differently with identical receptors or that they associate with different receptors. This assumes that the N-methyl compound (172a)

interacts with receptors in an identical fashion but differs in its mode of interaction from the corresponding N-(cyclopropylmethyl) analogue (172b).



(172)

a. R = Me

b. R = $-CH_2-c-C_3H_5$

4.2 Synthesis of a novel tetracyclic benzomorphan; 2,8-bridged benzomorphan derivative (165).

The synthesis of 165 was achieved by the sequence of reactions outlined in Figure 39. The additional ring was constructed via the intermediate 8β-chloroacetamido-6,7-benzomorphan (162).

Examination of Dreiding molecular models of 8α- and 8β-chloroacetamido derivatives (162 & 163) indicated that the β-isomer is favourably disposed sterically for cyclization by intramolecular displacement of halogen by the tertiary ring nitrogen, ie. intramolecular quaternisation. Attempted ring closure of 162 by heating in boiling acetone was

unsuccessful and starting material was recovered. When the ring closure was attempted in higher boiling diisopropyl ketone, decomposition of the 8β-chloroacetamido-6,7-benzomorphan resulted. Failure may have been due to the relatively poor leaving properties of the chlorine.

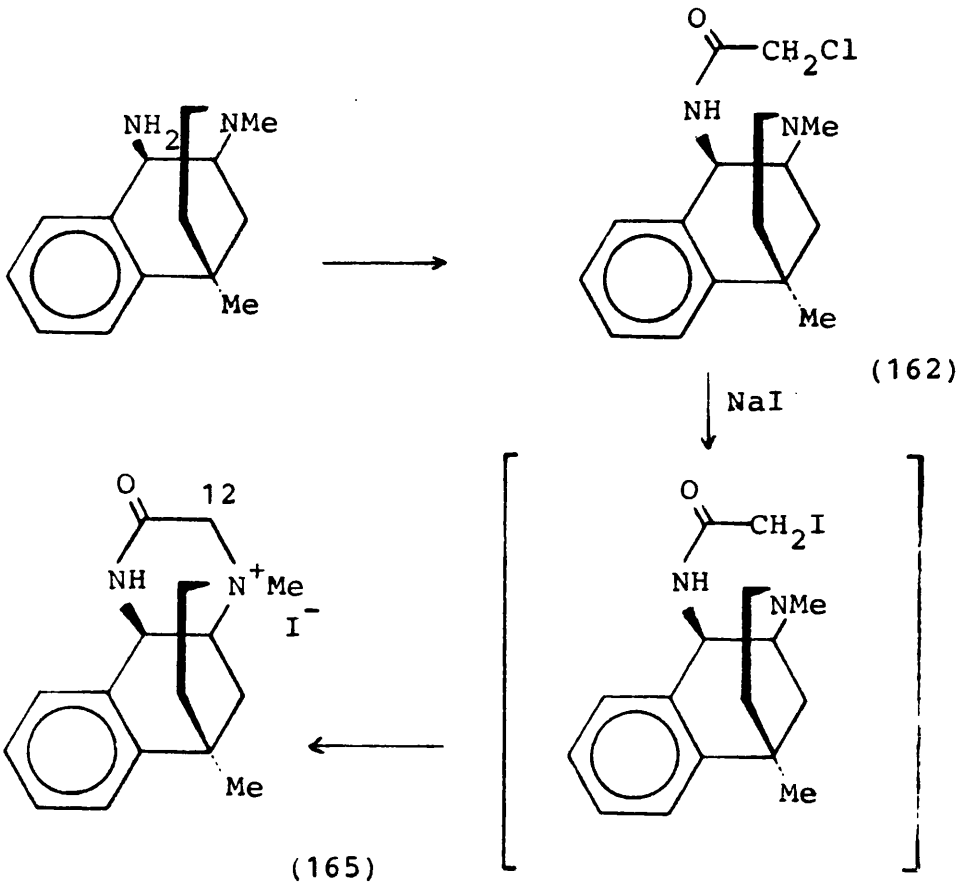


Figure 39

The mechanism of amines reaction with alkyl halides and particularly of quaternisation reactions have been reviewed by Streitwieser[189] and Ingold[188]. Reactions generally proceed via an uncomplicated SN_2 process, and usually follow a second-order rate law. The rate depends upon the nucleophilicity of the amine, the

solvent polarity and the leaving characteristics of the displaced group.

The most notable structural features of the SN_2 mechanism is derived from the fact that it requires a new bond to be formed at the same time as the old bond is broken in order to facilitate the latter process. The accommodation of five groups around carbon, two of them being partly bonded to the centre by four electrons, results in a highly congested transition state. A consequence of the crowded nature of the transition state is that the introduction of bulky groups at the reaction centre is generally associated with a decrease in reaction rate. Bimolecular nucleophilic substitution is usually accomplished by inversion of configuration[190].

Theoretically, one would expect that electron-release towards the centre at which replacement was occurring could increase the ease of separation of the departing halogen, but could at the same time reduce the ease of attack by the nucleophile. In fact the transition states for SN_2 substitution are often very closely balanced in their response to polar effects; the rate can be enhanced by either electron-releasing or electron-withdrawing conjugative effects, and it can be diminished by either electron-withdrawing or electron-releasing inductive effects. The failure of the 8β-chloroacetamido-6,7-benzomorphan (162) to form a bridged quaternary compound (165) may be

explained in terms of a polar effect. The amide group, which is powerfully electron-withdrawing by the inductive effect but a weakly electron-releasing by the conjugative effect, will reduce the ease of separation of the departing halogen.

The ease of replacement of halogen amongst the alkyl halides parallels the relative leaving group ability of the anion in an SN_2 reaction, ie. $I^- > Br^- > Cl^-$. High polarisability makes I^- both good entering and a good leaving group, and it is thus often used as a catalyst to promote an otherwise slow displacement reaction. The presence of iodide ion generates the organic iodide *in situ* by halogen exchange[190].

The conversion of β-chloroacetamidobenzomorphan (162) into the corresponding iodoacetamido derivative (173) may be accomplished by treatment with sodium iodide. A cold solution of 8β-chloroacetamide (162) in acetone added to a stirred ice-cold solution of sodium iodide in acetone resulted in the precipitation of sodium chloride which was removed and evaporation of the solvent gave the required 2,8-bridged quaternary compound (165). No intermediate 8β-iodoacetamide (173) was isolated; intramolecular nucleophilic displacement of halogen ion by the ring nitrogen and ring closure had occured *in situ*.

This type of intramolecular attack of the nitrogen atom on the halogenated carbon to form 3-,4-,5-,6- and 7 membered cyclic ammonium ions has been studied by Sølomon[191]. The ease of formation of products as it

relates to ring-size was reviewed by Bennett[192]. The stereochemical course of these intramolecular reactions has been found to be similar to that of an intermolecular SN_2 process, and proceeds with formal inversion of configuration of the centre of displacement. In the intramolecular process, only one molecule is formally involved in the rate-determining step, and thus it could be described as an SN_1 process.

The interchange of one halogen with another is an equilibrium process but iodides may be prepared from chlorides because of the fact that sodium iodide is soluble in acetone whereas sodium chloride is not. When an alkyl chloride is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride.

$$RCl + NaI \rightleftharpoons RI + NaCl$$

An examination of the NMR and mass spectra of 8β-chloroacetamide (162) and the quaternary compound (165) indicated that the desired cyclisation had occurred. The C_1 proton, C_3 protons and N-Me protons of 162 occurring at 3.1, 2.0 and 2.6 ppm respectively are shifted to lowerfield in the cyclic quaternary salt (165) due to the strong deshielding effect of the cationic nitrogen. The signal of the C_1 proton was seen as a multiplet at 4.33 ppm, N-Me protons as a singlet (3H) at 3.32 ppm and C_3 protons as a

quartet (J≈5 Hz) centred at 4.30 ppm. The benzylic proton and C_{12} protons of the quaternary compound appeared as a multiplet centred at 5.18 ppm and a singlet at 3.41 ppm respectively. The chemical shifts of these protons would be expected to be similar to the corresponding signals in the 8β-chloroacetamido compound (162).

Many significant differences were observed between the mass spectra of 8β-chloroacetamide (162) and the cyclic quaternary salt (165). The mass spectrum of 165 gave a weak M^+ at M/Z 256, corresponding to a molecular formula $C_{16}H_{22}H_2O$. The peak at M/Z 242 due to loss of methyl iodide is strong (60%) relative to that in the 8β-chloroacetamido derivative (162). The base peak in the spectrum of 165 is at M/Z 59 as oppose to M/Z 70 in the spectrum of 162.

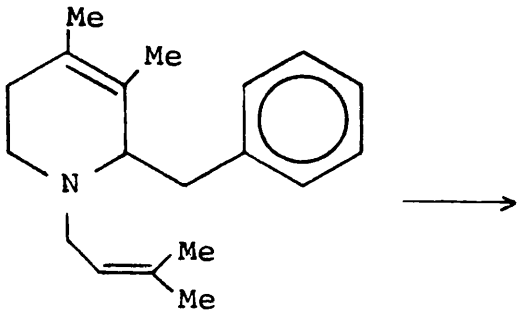
The stereochemistry of 8β-chloroacetamide (162) is confirmed by its successful cyclization to the bridged compound 165. All attempts to cyclize the 8α-chloroacetamide (163) under similar conditions proved to be impossible as anticipated on steric grounds. The reaction of 8α-chloroacetamide (163) with sodium iodide in acetone yielded a very polar product which could not be extracted into ether or dichloromethane. A mass spectrum of the product crystallized from ethanol gave M^+ at M/Z 305. The PMR spectrum was complex and the compound could not be identified.

Several different hypotheses have been advanced to explain the roles of N-substituents in conferring agonist or antagonist activity on opiate analgesics. Snyder et al[55] have proposed a receptor model to explain agonist and antagonist properties on the orientation of N-substituents, and suggested that the N-substituent was confined to axial positions in the active conformation of antagonists. However, both axially and equatorially confined substituents have been identified in a number of homobenzomorphan agonists[59,60]. Kolb[62] has postulated that the primary action on a receptor by an opiate is through its lone pair and that the direction of the N-non bonding electron lobe is responsible for agonist or antagonist activity. The novel tetracyclic benzomorphan derivative (165) has a rigid conformation and fixed N-substituent and thus could be useful tool for the analysis of the opiate and its receptor interaction.

While this work was in progress, Shiotani and Kometani[106] described the synthesis of two 2,8-bridged benzomorphan derivatives (Figure 22; 92 & 95). These compounds displayed no significant analgesic activity.

Earlier, Kimura et al[173] had reported that cyclization of the tetrahydro compound (174) with a Lewis acid gave a novel tetracyclic benzomorphan (175). Such compounds were found to be potent analgesics with low toxicity in mice. Recently, Nozaki et al[174] investigating chemical features necessary for opiate

agonist and antagonist activity synthesised the tetracyclic benzomorphans 176 and 177. No experimental details or biological data were reported.



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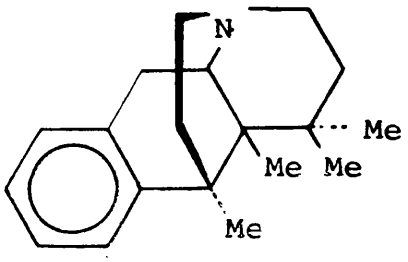

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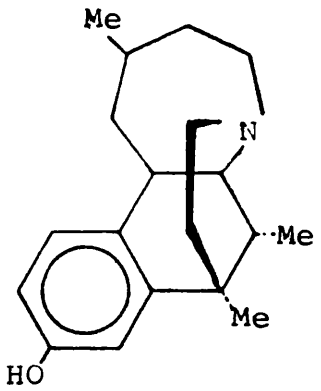

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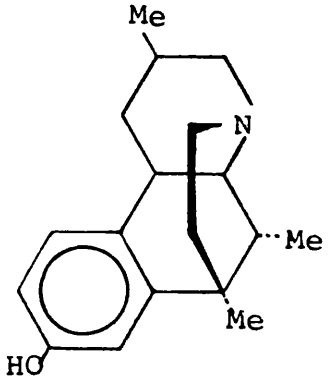

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CHAPTER FIVE

8-AMINOMETHYL-2,5-DIMETHYL-6,7-BENZOMORPHAN AND RELATED COMPOUNDS

CHAPTER FIVE

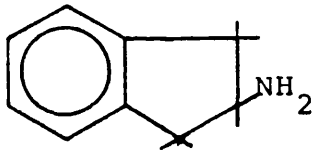
8-AMINOMETHYL-2,5-DIMETHYL-6,7-BENZOMORPHAN AND RELATED COMPOUNDS

5.0 Introduction.

The search for effective centrally acting analgesic agents devoid of dependence and respiratory depressant properties has led to an unusually rich selection of compounds upon which to base proposals for the structural requirements for opiate activity. Most structures exhibiting such activity fit a common pattern in possessing a basic nitrogen atom separated by a two carbon unit from an aromatic ring[3,8-11,21,50,53,54,61,64].

Analgesic activity has been demonstrated in simple amines like β-phenylethylamines and their rigid analogues, 2-aminoindane derivatives[193]. Some 2-aminoindanes (eg. 178) exhibited high activity and proved effective up to the clinical evaluation stage, but the occurrence of stimulation and hypertension precluded their use in therapy[193]. N,N-Dimethyl-1,2-diphenylethylamine (179) has been reported to be approximately half as active as morphine as an analgesic[194], and analgesic activity has been reported in tetralins and bridged tetralins (eg. 180) possessing an excocyclic amino function[195]. The possible structural similarity of met^5-enkephalin to morphine by virtue of their phenylethylamine unit has been pointed out[68]; however it has been recently demonstrated that the conformation of this moiety in receptor-bound conformation of the peptide is different

from that present in the rigid morphine molecule[196].



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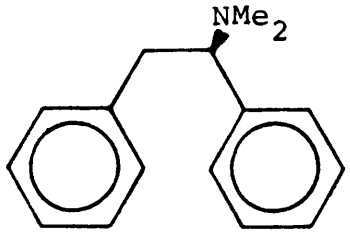

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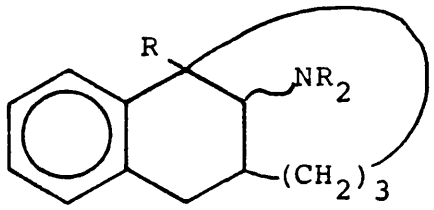

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The presence of a β-phenylethylamine moiety is an essential feature of molecules with high analgesic activity. It has been postulated that this moiety is important for stereochemically controlled binding of analgesics at the receptor site[138]. The importance of the nitrogen to phenyl distance in structure-analgesic activity relationships has been described recently[137-40]. If it is assumed that a cationic nitrogen binds with an anionic site of opiate receptors and that the aromatic ring interacts with the lipophilic site to form a drug-receptor complex then the binding affinity would be greatly affected by the nitrogen to phenyl distance within the analgesics. It is noteworthy that structural modification of 6,7-benzomorphans made by

changing the position of nitrogen decreases the analgesic activity[137-140].

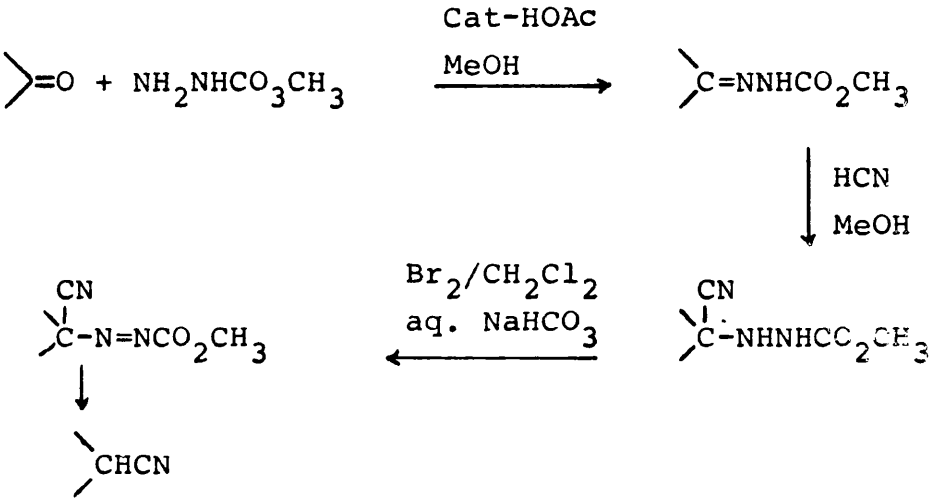
Several compounds possessing interesting analgesic and narcotic antagonist activity have evolved from studies on the 6,7-benzomorphan nucleus. Early work on structure-activity relationships have been addressed mainly to the effect of oxygen, hydroxyl, alkyl or aryl substituents in various positions of the molecule and variation of N-substituents[3,61,93].

In order to investigate further structure-activity relationships in the 6,7-benzomorphan series we decided to explore the effect of introducing an aminomethyl group at the 8 position. This modification creates a second phenylethylamine moiety and may effect binding at an analgesic receptor. In this chapter the synthesis of 8-aminomethyl-6,7-benzomorphan (184) and its derivatives is described.

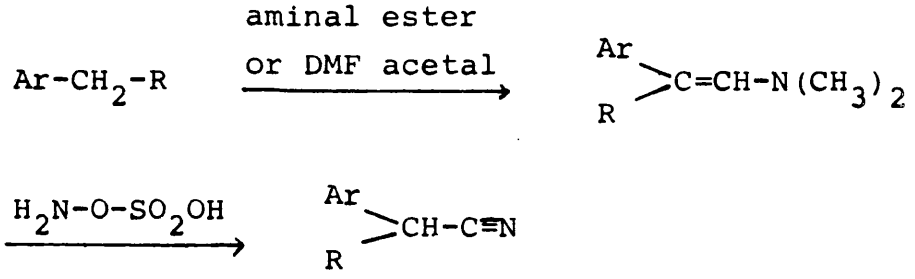
5.1 The oxidative decyanation of 8α-cyano-2,5-dimethyl-6,7-benzomorphan: an attempt to prepare 8β-cyano-2,5-dimethyl-6,7-benzomorphan.

Cyano groups rank highly in their utility among the many synthetically useful functional groups of organic chemistry[128]. Their reactivity makes possible transformation into carbon-oxygen functional groups at both ends of the oxidation scale. Nitriles are readily obtained by a variety of reactions[129]. The dehydration of carboxylic acid amides or aldoximes are among general methods of formation of nitriles.

Other general methods of synthesis involve the substitution of a suitable leaving group in an organic compound by a cyano group[128,129]. The conversion of ketones into nitriles by base induced decomposition of methyl dialkylcyanodiazone carboxylate has been reported by Ziegler et al[198] (as shown below).



Recently, Biere et al[199] reported the synthesis of nitriles from hydrocarbons but no experimental data were given. The procedure involved the condensation of the aromatic compound possessing an activated methylene group with dialkyl formamide acetal or aminal esters to give the enamines which on treatment with aqueous hydroxylamine-O-sulphonic acid yielded directly the nitrile.



The 8α-cyano-2,5-dimethyl-6,7-benzomorphan (121) was prepared by reaction of ketone (100) with a freshly prepared solution of tosylmethyl isocyanide (TOSMIC) in dimethyl sulphoxide containing potassium tertiary butoxide as described earlier (Section 2.4). The conversion was completely stereoselectively giving 8α-cyano-benzomorphan (121) as the only epimer detected. This fact may be explained in terms of attack of the large TOSMIC anion occurring only at the more accessible α-face of the 6,7-benzomorphan. The β-face of the 6,7-benzomorphan is sterically hindered due mainly to the iminoethane bridge between carbons C_1 and C_5.

The use of TOSMIC in the conversion of ketones to nitriles is reported to afford both isomers[131]; for example 2-norboranone gave both endo- and exo-2-cyanonorborane. The ratio of isomers was suggested to reflect thermodynamic control through the carbanion intermediate[131] (Section 2.4, Scheme 4,9). In view of this the exclusive formation of 8α-isomer (121) was rather surprising. The absence of the β-isomer may be explained in terms of the steric hindrance caused by the long length of the cyano group in the 8β-cyano-benzomorphan.

The stereochemistry of the 8α-cyanobenzomorphan (121) was determined from the ^1H NMR chemical shift and coupling constant between C_1-C_8 protons. The cyano group is a strong electron withdrawing substituent, and its inductive effect is considerably enhanced by

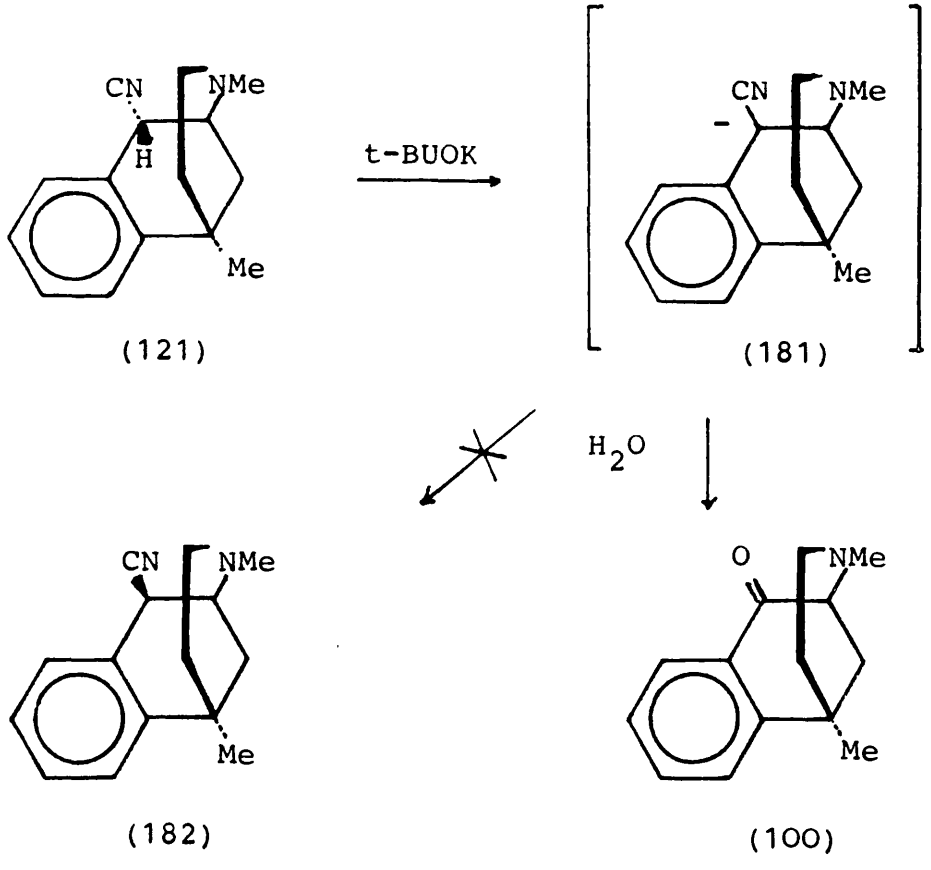
resonance interactions. The benzylic proton, H_β, appears as a singlet at 4.16 ppm with J=2 Hz. The C_1 proton of the α-cyano compound appears at lowfield (3.42 ppm) relative to that of α-amine (127, 2.90 ppm). This paramagnetic shift may be due to C_1-H being held in the deshielding zone of the anisotropic nitrile.

It is reasonable to assume that the other methods will also give 8α-cyanobenzomorphan (121) instead of β-cyano derivative (182). In this study an attempt was made to prepare 182 by racemisation of the α-nitrile (121) via a carbanion. The benzylic proton of the 121 is relatively acidic and may be removed by treatment with base. The acidity of the C_8-H bond is attributed to a combination of the inductive electron-withdrawing ability of the cyano substituent and the ability of this substituent to delocalize the negative charge remaining when the proton has been removed. The aryl ring provides considerable additional stabilization for the carbanion. Nitrile (eg. 121) can be converted to its anion by treatment either with relatively strong bases in aprotic solvent or with anhydrous alcoholic solution of a metal alkoxide[200].

In theory, a carbanion could assume a pyramidal Sp^3 or a planar Sp^2 configuration depending on substituents. The pyramidal configuration with the unshared electron pair occupying the fourth Sp^3 orbital would resemble the amine with which they are isoelectronic. Since carbanion (181) has substituents capable of conjugative delocalization of the electron pair it will

probably be planar Sp^2, in order to allow the maximum orbital overlap of the p orbital with those of the substituents[201]. Proton from the solvent may now come to either face of the flat carbanion producing both α- and β-nitriles.

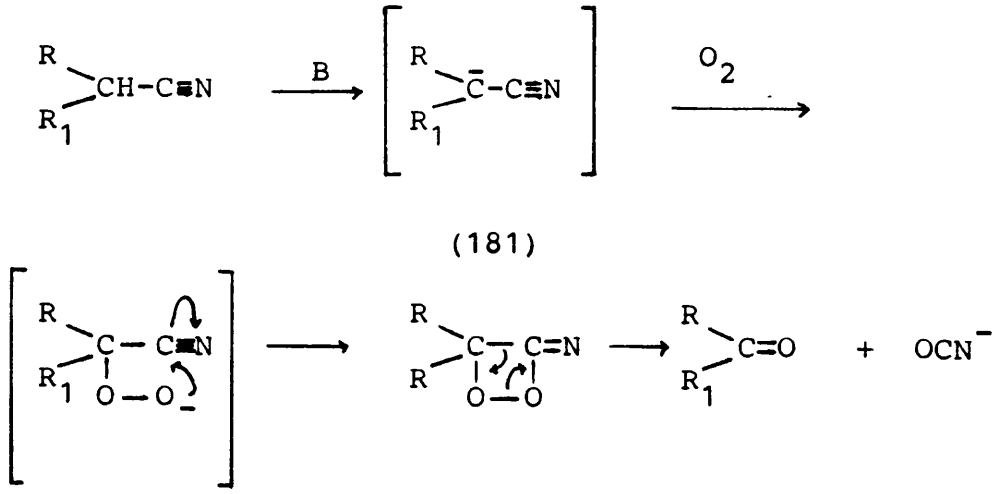
The 8α-nitrile (121) was treated with potassium-t-butoxide in dry tertiary butanol[200] at room temperature for a few hours and the resulting mixture was poured into ice water and extracted with dichloromethane. This surprisingly afforded 8-oxobenzomorphan (100), identified by IR, NMR, RF and GLPC peak enhancement with an authentic sample.



(121) (181) (182) (100)

In order to investigate the mechanism of this transformation the reaction was repeated with sodium hydride in an aprotic solvent (THF) and this too yielded 8-oxo compound (100). However, when the reaction was carried out in a strict nitrogen atmosphere and progress was monitored by TLC, no 8-oxobenzomorphan (100) was formed for up to four hours. This clearly suggested the role played by atmospheric oxygen.

The formation of 8-oxo-6,7-benzomorphan may be explained by the mechanism in Scheme 10. This mechanism involves the formation of a nitrile anion (181) by the tertiary-butoxy anion, which is followed by the attack of oxygen on the carbanion to afford α-cyanohydroperoxide (183). Subsequent exposure of this hydroperoxide to aqueous potassium hydroxide affords the ketone.



(181)

(183)

Scheme 10

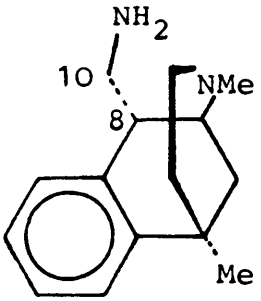
The potassium-t-butoxide in tertiary butanol has been used for autoxidation of ketones, aldehydes and esters[202,203]. The reactions were assumed to proceed via α-hydroperoxide intermediates although these intermediates were not isolated. However α-hydroperoxides of 20-keto steroids have recently been isolated from the product of autoxidation in potassium-t-butoxide and t-butanol[204].

The procedure described above allows direct introduction of an oxygen substituent to a nitrile. Previous procedures which accomplish this transformation effect the oxidation of nitriles to cyanohydrin via intermediate α-iodo[205] and α-thiophenoxynitriles[206] and subsequent conversion of the cyanohydrins to ketones. Few procedures allow for the direct introduction of an oxygen substituent onto a nitrile. However, Watt and Selikson[207] have recently reported general oxidative decyanation for the synthesis of ketones from secondary nitriles.

5.2 Preparation of 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan. Reduction of 8α-cyano-6,7-benzomorphan (121).

The lithium aluminium hydride reduction of 121 was complicated in that it tended to undergo other reactions and gave a low yield of the required 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan (184). Thin layer chromatography of the resulting crude

product indicated a mixture consisting of five or six components, two of which gave ninhydrin positive reactions..The infra-red spectrum had a distinct carbonyl absorption band at 1675cm^{-1}, and amine bands at 3480cm^{-1} and at 1603cm^{-1}. PMR examination indicated the presence of two major components in 1:1 ratios. These components were identified as 8α-aminomethyl-benzomorphan (184) and 8α-aldehyde (185). Attempted column chromatographic separation was unsuccessful and only impure 184 was isolated.



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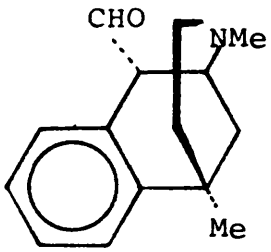

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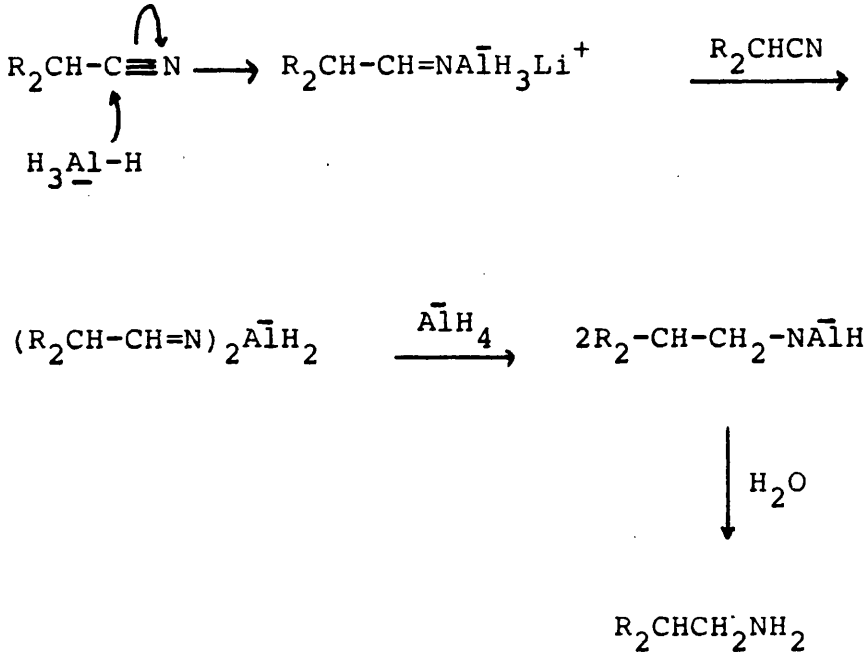
The reducing action of LAH has been extensively studied[143-145,209-212]. The mechanism of lithium aluminium hydride reduction involves the transfer of hydride ion from the aluminohydride ion to the nitrile carbon atom, and it is known to proceed via an aldimine stage (Scheme 11). There is considerable evidence indicating that each successive hydrogen ion transfer takes place more slowly than the one before[143]. On hydrolysis the aluminium atom is replaced by hydrogen

supplied by the hydrolysing agent.



Scheme 11

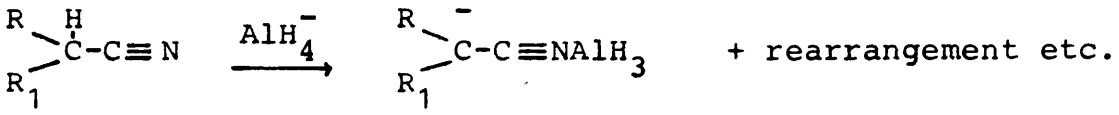
In the usual reaction conditions intermediate imines are further reduced to amines, but they have been hydrolysed *in situ* to the aldehyde. The selective hydride reduction to the imine stage has been achieved by variation of the reaction conditions, the indirect synthesis and variation of the reducing hydride reagent[213]. Hindered nitrile groups for example in angular positions in steroids are reduced by LAH either to aldehydes or to the corresponding amines depending on the stereochemistry of the nitrile group[214].

LAH reduction usually reduces a nitrile to the primary amine probably due to the ease of the reduction of the intermediate imine. In this work it appears that reduction proceeds as far as the imine but is halted

perhaps partly because of formation of the insoluble lithium aluminium salt of the imine. This salt is then hydrolysed to the aldehyde in the course of isolation. The steric and electronic characteristics of the phenyl group will stabilize the initial imine derivative permitting the isolation of the aldehyde. The inductive influence of the neighbouring carbon centres and the large steric requirement of the 8α-cyanobenzomorphan (121) will also reduce the rate of nucleophilic attack at the imine carbon. Thus the first hydride addition will be favoured over the second, resulting in aldehyde formation. It has been suggested that lithium ion may become coordinated to the nitrogen atom of the imine intermediate and this would further assist in protecting the double bond from a second hydride addition.

Many nitriles are reduced satisfactory with LAH to primary amines and the reaction has been adequately reviewed[145,210,215]. The effective reducing agent is AlH_4^- which acts as powerful hydride ion donor; such being the case it also preferentially abstracts proton from compounds with active hydrogen. Thus, LAH is a very strong base in addition of being a powerful reducing agent. Hydrogen evolution representing attack by the nucleophilic reagent on the active hydrogen of the α position has been described in a number of reactions with LAH[211,212]. This is believed to be responsible for the decreased yields encountered in

this reduction of 8α-cyano-6,7-benzomorphan. The carbanion (186) formed may undergo further abnormal changes involving possibly rearrangements, ring opening and condensation leading to a multicomponent mixture.



(186)

It has been reported that the undesirable side reaction in the reduction of nitriles can be diminished by carrying out the reaction in tetrahydrofuran instead of in ether, by employing lithium trimethoxyaluminohydride[213] or by the use of a mixture of aluminium chloride and LAH[209]. The general effect of the addition of aluminium chloride is to lower the reducing power of LAH and in consequence to produce reagents which are more specific for particular reactions. The use of this 'acidic hydride' is known to reduce nitriles containing active hydrogen completely in good yields without liberation of hydrogen[209].

Reduction of 8α-cyanobenzomorphan (121) with the mixture of aluminium chloride and LAH gave a multicomponent mixture containing some of the desired amine. PMR and IR spectra were similar to those of the product obtained from LAH reduction and the reaction was not examined further.

Nitriles have been reduced to amines by sodium and

alcohol but extensive reductive cleavage of the cyano group occurs especially with phenyl or benzyl derivatives[216]. It was predicted that the presence of active α hydrogen in the nitrile (121) would further complicate the reaction, as was evident from the earlier attempt at racemization under related conditions. Consequently no attempt was made to employ this method.

The catalytic hydrogenation of nitriles to primary amines has been the subject of many investigations because good yields are frequently difficult to obtain. The difficulty apparently arises because the reduction proceeds stepwise through the imine, some of which condenses with the primary amine already formed and ultimately leads to secondary amines[218,219] (Scheme 12). Further, the imine products are catalyst poisons as they bind with active surface via the unshared nitrogen electron.

$$R\text{-}C{\equiv}N \xrightarrow[\text{catalyst}]{H_2} R\text{-}CH{=}NH \xrightarrow{H_2} R\text{-}CH_2\text{-}NH_2$$

$$R\text{-}CH_2\text{-}NH_2 + R\text{-}CH{=}NH \rightleftharpoons RCH_2NH\text{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{-}R \rightleftharpoons$$

$$R\text{-}CH_2N{=}CH\text{-}R + NH_3 \xrightarrow[\text{catalyst}]{H_2} R\text{-}CH_2NH\text{-}CH_2\text{-}R$$

Scheme 12

Rosenmund[128] has suggested carrying out the hydrogenation in acetic anhydride solvent in order to trap the primary amines as their acetamides. The yield of primary amine is also increased at the expense of side products by using as solvent ethanol containing some hydrochloric acid[128]. Hydrogenation in acetic anhydride in the presence of Raney nickel catalyst and a basic cocatalyst is reported to be very effective for reduction of a variety of nitriles to primary amines[220]. Recently Freitelder has described the catalytic hydrogenation of a nitrile under mild conditions with rhodium catalyst[221].

We prepared the 8-aminomethylbenzomorphan (184) in good yields by the hydrogenation of the nitrile (121) in ethanol containing a small amount of chloroform over a platinum oxide catalyst. The reduction was carried out at room temperature and low pressure (3 atm). The hydrogenolysis of the chloroform produces small quantities of hydrogen chloride which combines immediately with the amine as it forms by reduction and leads directly to the corresponding amine hydrochloride[217]. An important advantage of the procedure used in this work lies in the fact that it provides a method for the preparation of amine hydrochloride from 8α-cyanobenzomorphan which might be unstable in acidic media. It also eliminates the acylation and the subsequent required hydrolysis is avoided.

Thin layer chromatographic analysis (silica gel)

of the reduced product (184) showed only one spot. That the reduction had occurred was indicated by absence of a nitrile band and the presence of a typical N-H stretching band at 3380cm^{-1}. The ^{1}H NMR spectrum of the free base of the reduced product was consistent with the expected amine (184). The spectrum showed the benzylic proton signal at 3.16 ppm, a triplet for the C_1 proton at 2.87 ppm ($J \sim 4$Hz) and a multiplet centred at 2.85 ppm for the C_{10} protons. It is noteworthy that the C_1 proton of 8α-cyano derivative (121) which appeared at 3.42 ppm was shifted to 2.87ppm in the amine (184).

5.3 Some reactions of 8α-aminomethyl-6,7-benzomorphan.

5.3.1 Preparation of 8-(acetoamidomethyl)-, 8-(cyclopropionamidomethyl)- and 8-(phenylacetamidomethyl)-2,5-dimethyl-6,7-benzomorphan.

The synthesis of the title compounds from 8α-aminomethylbenzomorphan is outlined in Figure 40. Target amides (187, 188 & 189) were prepared essentially in the same manner as that described for 8-amino-2,5-dimethyl-6,7-benzomorphan (Section 3.2.1), namely by reacting the amine with the required acid chloride in the presence of a base. Thus, the reaction of the amine (184) with acetyl chloride and cyclopropanecarbonyl chloride in dichloromethane containing a mole of triethylamine gave acetamidomethyl- and cyclopropionamidomethyl

derivatives (187 & 189) respectively, as amorphous products. These compounds were crystallized from ethanol as hydrochloride salts.

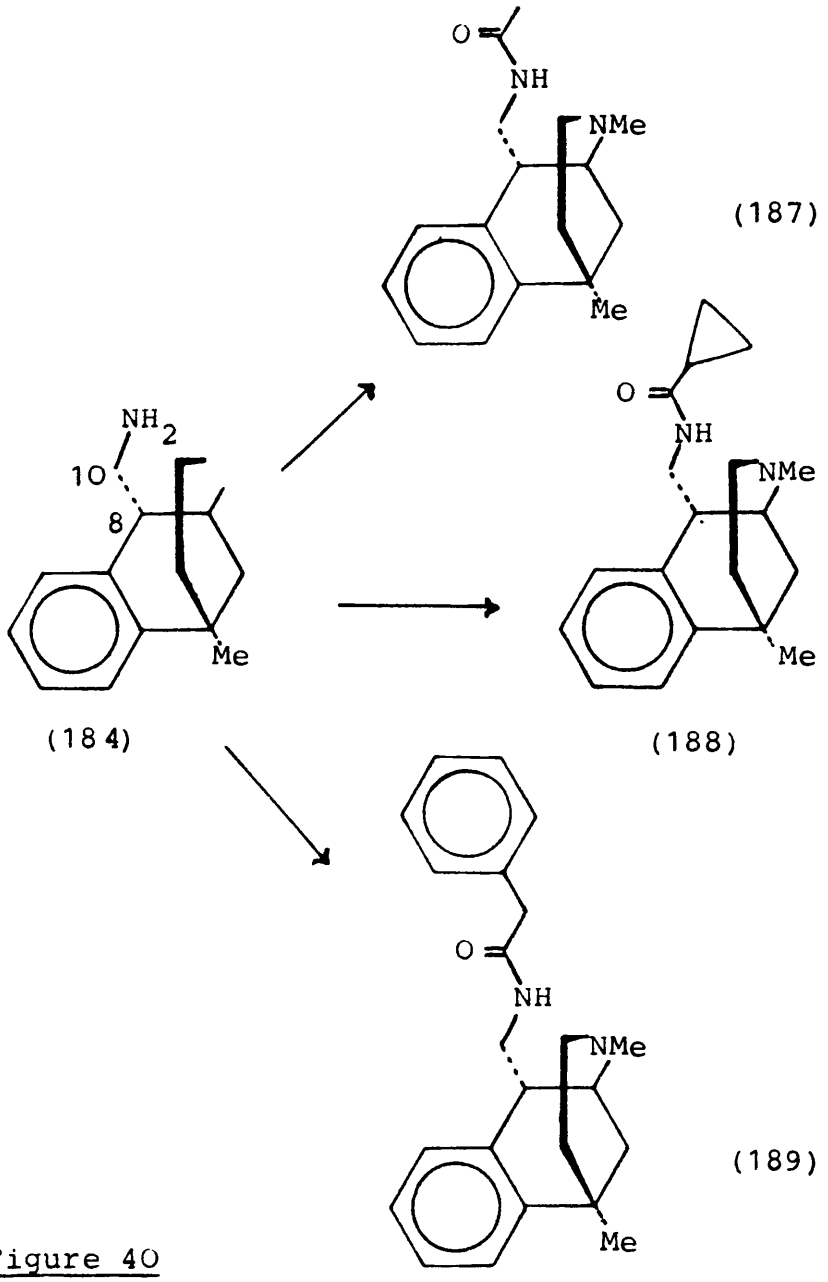


Figure 40

The acylation of the amine (184) with phenylacetyl chloride was carried out in aqueous methanol in the presence of potassium carbonate. The use of aqueous methanol is effective because the rate of solvolysis of phenylacetyl chloride is extremely slow in aqueous

methanol. Organic solvents such as ether or THF with a tertiary amine such as triethylamine have been used for this reaction. The phenylacetamidomethyl derivative (189) was purified by crystallisation from ethylacetate-petroleum ether.

These amides (187, 188 & 189) were identified by their NMR and infra-red spectra. Infra-red spectra displayed characteristic $\diagdown\!\!\diagup C{=}O$ and N-H stretching bands at $1640cm^{-1}$ and $3360cm^{-1}$ respectively. The N-H bending deformations of amides occurred at $1550cm^{-1}$. The $\diagdown\!\!\diagup C{=}O$ stretching band in 8α-(chloroacetamidomethyl)-6,7-benzomorphan (164) was displayed at a higher frequency ($1670cm^{-1}$) due to the presence of the electron withdrawing chlorine atom (Section 3.2).

The 100 MHz proton NMR of amides (187, 188 & 189) revealed complex but well resolved splitting patterns for the C_8 and C_{10} protons, and this was similar in all three derivatives. The C_{10} protons appeared as a double doublet instead of the expected doublet after D_2O exchange of the amide proton. This is possibly due to these protons being adjacent to an asymmetric carbon centre (C_8). A molecule in which a methylene group is adjacent to an asymmetric carbon centre forms an AB-system, a phenomenon which is well known[233]. The N-methyl protons in phenylacetamide (189) is shifted 0.18 ppm (2.18 ppm) compared with its normal position (2.36 ppm) in acetamido- and cyclopropionamido derivatives (187 & 188). Several other differences in

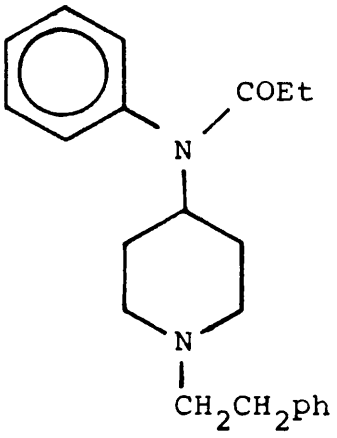
the NMR of the amides were noted. The C_1 bridgehead proton, N-H proton and, C_8 benzylic and C_{10} protons of 187 and 188 all absorb at lower field (3.0, 6.36 and 3.04-3.8 ppm respectively) compared with that of 189 (2.7, 6.0 and 2.90-3.5 ppm respectively). The diamagnetic shift of these protons is probably due to the anisotropic effect of the aromatic ring of the phenylacetamido derivative. The aromatic region of 8α-aminomethylbenzomorphan (184) was observed as an apparent singlet whereas this region appears as a broad multiplet in the amides (187, 188 & 189) possibly due to the anisotropic effect of the carbonyl group on aromatic protons.

A number of basic amides, for example fentanyl (190), dextromoramide (191), are active analgesics and are in common clinical use. Fentanyl is a highly potent narcotic analgesic agent which is widely used in anesthesiology[39,222]. In vitro receptor binding studies have shown that this derivative possesses a very high opiate receptor affinity with K_1 values in the subnanomolar range. Lobbezzo et al[223] have reported that the replacement of the amide nitrogen in fentanyl by a carbon atom causes a complete loss of analgesic activity. It is generally acknowledged that oxygen function at C_4 in 4-phenylpipiridine serves as an additional binding site for drug receptor association.

The rationale behind preparation of the amides (187, 188 & 189) described here was because of their rigidity which may provide valuable information

regarding the location of binding site(s), and may furnish compounds of therapeutic importance.

In this connection it should be noted that a series of N-(aminoacid)-substituted benzomorphan derivatives (eg. 192) have been reported, recently, to possess opiate receptor binding activity[224]. The basic centre of the benzomorphan in these compounds was neutralized by an amide linkage and the new basic centre of the amino acid function was considerably displaced in space relative to the original basic centre. Based on classical structure-activity relationships[3] in the 6,7-benzomorphans such a displacement produces a considerable reduction of opiate binding activity.



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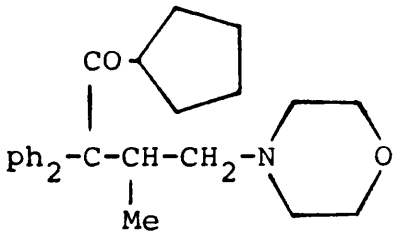

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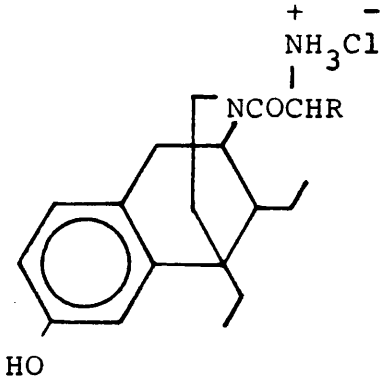

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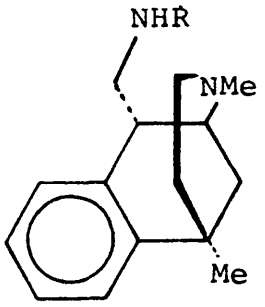
5.3.2 Synthesis of 8α-(ethylaminomethyl)-,8α-(cyclopropylmethylaminomethyl)- and 8α-(phenylethylaminomethyl)-2,5-dimethyl-6,7-benzomorphan.

Nitrogen substituents on opiates play a central role in determining the relative agonist/antagonist potencies of these molecules. For example, a narcotic antagonist component of action may be incorporated into a morphine derived narcotic agent by replacement of the N-methyl group with moieties such as allyl, cycloalkyl methyl[26,61] or tetrahydrofurfuryl[28-30]. The potency raising effect of the N-phenylethyl group is well established. The phenylethyl normetazocine (17, R=CH_2CH_2ph) is about 10 X more potent than metazocine (17, R=CH_3) and has high affinity for the receptor[138].

With the desired amine (184) at hand, the various 8α-alkylaminomethyl-6,7-benzomorphans (Figure 41) were prepared for pharmacological evaluation. These compounds (193, 194 & 195) were synthesized following an established literature procedure for the acylation of the amine and the subsequent reduction of the amide[93,168]. Thus, amine (184) was treated with the appropiate acid chloride in the presence of a hydrogen acceptor to afford amides and the intermediate amides were reduced with LAH in ether or THF. The reduction proceeded smoothly to yield the corresponding N-alkylated 8α-(aminomethyl)-6,7-benzomorphans (193, 194 & 195) in poor to good yields. The absence of a PMR signal for the amide proton and the loss of the carbonyl stretching band in the

infra-red spectra indicated that reduction had occurred.

All amine hydrochlorides were prepared by treating an ether solution of the free amine with ethereal hydrochloric acid. The hydrochlorides were crystallized from ethanol-ether.



(193) R = $-CH_2CH_3$

(194) R = $-CH_2$-cyclopropyl

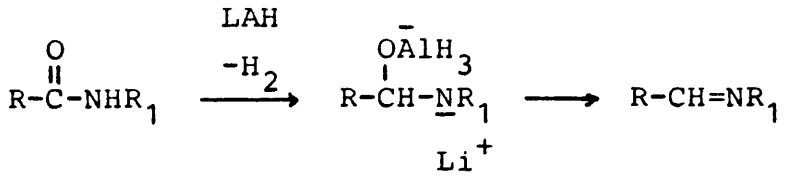
(195) R = $-CH_2CH_2$-phenyl

Figure 41

The direct alkylation on the nitrogen with alkyl halides[26] is inapplicable as the reaction will lead to mixtures of amines and quaternary ammonium salts. Alkylation of amines by the carboxylic acid-sodium borohydride method of Marchini *et al*[227] is also inapplicable as it is likely to be complicated by the formation of tertiary amines.

The reduction of amides to amines is believed to proceed by an initial reduction to a geminal amine alcohol derivative (196), following by elimination and subsequently reduction of the resulting imine[219] (Scheme 13). Newman *et al*[225] have presented evidence indicating that the reduction of unsubstituted amides

with LAH proceeds by the initial dehydration of the amide to a nitrile.



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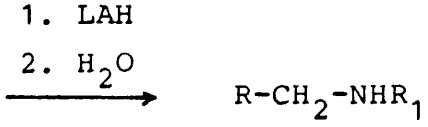


Scheme 13

It is suggested that during the reduction of an amide by LAH, there is a competition between the cleavage of the carbon-oxygen bonding leading to an amine and the rupture of the carbon-nitrogen bond leading to an alcohol[145,146]. This competition is markedly influenced by both the steric and electronic character of the amide group, and the conditions of reaction as well as by the amount of hydride[146].

The structure of the amines (193, 194 & 195) were clear from their spectral properties. IR spectra of the free amines exhibited typical N-H stretching absorption bands at 3340cm^{-1}. PMR spectrum of the 8α-ethylaminomethyl derivative (193) in $CDCl_3$ exhibited a typical triplet (1.10 ppm, J ~ 8Hz) for the methyl of the ethylamino group. The spectrum of 8α-cyclopropylmethylaminomethyl derivative (194) exhibited

a broad multiplet in the 0-0.7 ppm region for the cyclopropyl group. A multiplet centred at 0.5 ppm was assigned to the proton at the tertiary carbon atom of this group and a doublet at 2.56 ppm was assigned to the methylene α to cyclopropyl group. The methylene located α and β to the 2^{o} amino function ($PhC\underline{H}_2C\underline{H}_2NH$) in 195 appeared as a complex multiplet in the 2.6-3.00 ppm region. Chemical shifts of these protons are, as expected, influenced by the inductive effect of the phenyl ring. The vicinal couplings between the amine proton (N-H) and the protons on adjacent carbons was not observed in the spectra.

CHAPTER SIX

STEREOCHEMICAL STUDIES OF 8-SUBSTITUTED 6,7-BENZOMORPHANS AND THEIR DERIVATIVES BY ^{1}H AND ^{13}C NMR SPECTROSCOPY.

CHAPTER SIX

Stereochemical studies of 8-substituted 6,7-benzomorphans and their derivatives by ^{1}H and ^{13}C NMR spectroscopy.

6.0 PMR studies.

6.0.1 Introduction.

NMR spectroscopy has been extensively used in the field of medicinal chemistry both from analytical and structural aspects. Its great value lies in the detailed structural information it can provide, not only that concerning gross features but also fine points of molecular geometry[228,229]. Such information is of importance because it may lead to better understanding of the way in which molecules interact with their receptors.

There have been several reports upon the PMR features of benzomorphan and its derivatives[22-24,33,40]. The original assignment of α-cis and β-trans 5,9-dimethyl-6,7-benzomorphan was based on the PMR data[22], and was confirmed by x-ray crystallography[109]. The C_9-methyl in the α-isomer is about 0.5 ppm higher field than the β-isomer because it lies within the aromatic screening zone. It has been suggested that the proximity of the nitrogen lone-pair to the 9-Me group in the β-isomer may also, in part, be responsible for the α/β-9-Me shift difference[228].

A quaternization study of α- and β-metazocine has been investigated by PMR spectroscopy[22,24,33]. It has been proposed that skewboat populations are probably high in β-derivatives when protonated *in vivo* and that such conformers favorably influence drug receptor interaction[230]. X-ray analysis[231] of the α-N-allyl-5,9-dimethyl-6,7-benzomorphan has shown that ring B has a slightly distorted half chair conformation and that ring C possess approximately a chair form with the two methyl groups and the N-substituent in equatorial positions with respect to this ring.

The ^{1}H NMR characteristics of a series of 4- and 5-methyl-substituted benzomorphans were determined by Parfitt and Walters[40] in their study of the effects of steric crowding of nitrogen on analgesic activity. The 4-methyl appears strongly shielded at 0.6 ppm in contrast to the 3-methyl. This was rationalized by noting that when the piperidine ring is in the favourable chair conformation and the 4-methyl is equatorial, the latter lies in the shielding region of the fused benzene ring. It has been pointed out that since the 3-methyl has a normal field position at ~ 1.0 ppm, it also must be equatorial.

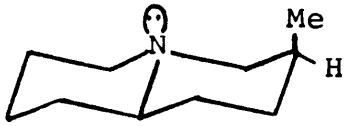
This chapter presents NMR data for a series of 6,7-benzomorphan derivatives. Although these data are of importance for identification and differentiation purposes, their great value lies in the evidence they provide of the configuration and conformation of the

various derivatives. The crucial influence of molecular geometry upon the activity of benzomorphan derivatives is well known, hence it is important that the stereochemistry of novel derivatives of potential activity in this respect is established.

6.0.2 Proton chemical shifts.

The proton chemical shift of 8-substituted-6,7-benzomorphans are shown in Table 11. 2,5-Dimethyl-6,7-benzomorphan (1,compound numbers 1-39 used throughout this discussion refer to the numbers in Table 11) is first discussed. The α-benzylic proton of 1 has a higher PMR chemical shift than the β-proton. This difference can be interpreted in terms of differential aromatic screening, the β-proton being deshielded because it lies within the aromatic deshielding zone. Yamaguchi et al[232] have attributed the downfield shift of the β-proton relative to the α-proton in dehydrodeoxycodeine-D to a shielding by the nitrogen atom. They claim that the benzylic protons are symmetrically disposed with respect to the aromatic nucleus. It deserves to be noted that the greater deshielding influence of the lone pair orbital upon axial than upon equatorial 3-Me substituents in trans quinolizidines (197) has been demonstrated[228].

A distinctive feature of the PMR spectrum of 8-oxo-6,7-benzomorphan (2) is the lowfield position



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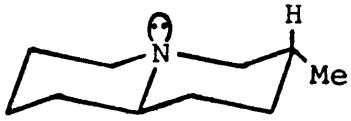


a-Me downfield by 0.27 ppm than e-Me signal.

of the C_4' aromatic proton (8.03 ppm) and the C_1 bridgehead proton (3.28 ppm). The lowfield absorption indicates the deshielding effect of the carbonyl function on neighbouring protons which lie in the nodal region of the >C=O bond. All aromatic protons in the 8-oxo compound (2) are deshielded in comparison to the resonance of the aromatic protons of unsubstituted 6,7-benzomorphan. The chemical shift difference between the aromatic protons result in a more complex aromatic signal than that of the benzomorphan (1).

The C_4' proton and C_1 proton signal for the oxime (3) appeared at 8.00 ppm and 4.41 ppm respectively. The particulary lowfield absorption of the C_1 proton even in comparison to the 8-oxobenzomorphan (2) is apparently due to the anisotropic effect of the hydroxyl group. The chemical shift of the C_1 proton indicates that it is <u>syn</u> to the hydroxyl group[120,121]. The geometry of the magnetic anisotropy associated with the oximino group is not known with certainty, although there have been several studies on this subject[120-124].

It has been suggested that the main deshielding effect on the α hydrogens arises from the proximity of the hydroxyl group or/and from the proximity of the unshared pair of electrons on nitrogen. The hydroxyl proton resonance of the oxime appears at 11.33 ppm.

The stereochemical assignment of the diastereoisomers (4 & 5) of aminobenzomorphan, obtained by reduction of the oxime, were deduced from the NMR evidence. The relative configuration of the amine was assigned from the vicinal coupling constants between the C_8- and C_1 protons. The dependence of vicinal coupling constants on the dihedral angle was first theoretically predicted by Karplus[142]. In the α-amine (4) the dihedral angle, measured in Dreiding models, between the $C_{8\beta}$ proton and C_1 proton is about 90°C while in the β-amine (5) the dihedral angle between the $C_{8\alpha}$ proton and vicinal proton (C_1-H) is about 30°C (Figure 32). Thus, according to the Karplus $\cos^2\theta/J$ relationship, $JH_{8\beta}H_1$ would be expected to be larger than $JH_{8\alpha}H_1$. This was observed in the spectra of α- and β-amines. The C_8 proton in the α-amine (4) appears as a singlet at 4.06 ppm (J=1-2Hz) as opposed to a doublet at 4.00 ppm (J=6Hz) in the β-amino isomer (5). The downfield shift of the benzylic proton in the amines compared to the unsubstituted benzomorphan is due to the inductive effect of the amino group. The C_1 proton signals in the amines are moved upfield to 2.96 ppm with respect to C_1 proton at 4.28 ppm in its precursor. This upfield shift is as expected with removal

of the inductive and anisotropic effect of the oxime group.

Close inspection of the NMR spectra of amines (4 & 5) revealed other relationships which appeared to be consistent with the assigned configuration of these diastereoisomers. Models of the 8β-amino-6,7-benzomorphan (5), indicate that the amine moiety lies close to the C_4' aromatic proton and its resonance should be different from other aromatic protons. This is confirmed experimentally; the β-C_4' proton appeared at downfield (7.60 ppm) relative to other aromatic protons (7.20 ppm). In the α-amine (4) the C_4' proton is further removed from the amino group and hence its chemical shift is closer to those of the other aryl hydrogens. Chemical shift differences among the aromatic protons are expected to be more pronounced in the β-amino isomer (5) with the result that the β aromatic signal was observed to be more complex than that of the corresponding α-amine.

There are other differences. For example the NH_2 singlet in the β-amine appeared at 2.04 ppm compared with 2.80 ppm in the α-amine. The downfield shift of N-H protons in the β-isomer may be due to their falling within the deshielding zone of the aromatic region. The other main spectral difference between the α- and β-amines was found in the chemical shift of the C_4 proton. The α-C_4 proton resonance is close to that of unsubstituted benzomorphan but the C_4 proton in the β-amine appeared at an unusually highfield (0.90 ppm). This

signal is almost coincident with α-9-methyl of 5,9-dimethyl-6,7-benzomorphan. The piperidine moiety in the β-amine is likely to be in a non-chair conformation. The marked upfield shift of the C_4 proton is probably caused by this slight difference in molecular geometry which could place the C_4 proton within the shielding zone of the aromatic ring.

The NMR spectrum of the 8α-cyano derivative (22) showed a number of general features similar to that described for the 8α-amine (4). The chemical shift and the coupling constant of the benzylic proton (C_8) indicated that the compound was the α-isomer. The C_8 proton singlet was located at 4.12 ppm, slightly downfield from this signal in the α-amine, because of the increased inductive effect of the nitrile group. The bridgehead proton resonance in the α-nitrile (22) at 3.44 ppm is considerably downfield ($\Delta\delta$ = -0.48 ppm) from its position in the spectrum of the α-amine (24) (2.96 ppm). This change can be ascribed to the anisotropic effect of the cyano group which is in proximity to the C_1 proton. Triple bonds such as C≡N have axial symmetry; a circulation is induced in the cylindrical shell of π-electrons by an external magnetic field so that a resultant field is developed. Nuclei along the axis of the triple bond will be shielded whereas nuclei in the area above and below will be deshielded relative to their normal position. The C_1 proton lies along the side of the triple bond and is thus deshielded.

The amide derivatives (6-13) obtained from amines (4,5) are compounds in which basicity of the nitrogen is diminished. The general characteristics of the amides' PMR spectra were similar to those of their precursors (4,5). The proton on the nitrogen atom of amides exchanges at slow rate and as a result it couples to the benzylic proton. The benzylic and the amide protons in α-acetamide (6) appeared as a doublet ($J \sim 10$ Hz) at 5.20 ppm and 5.90 ppm respectively. Deuterium oxide (D_2O) exchange of the amide proton reduces the doublet of the benzylic proton to the expected singlet. On the other hand, the β-acetamide (7) benzylic proton appeared as a doublet of doublet centred at 5.24 ppm with J=8 and 6 Hz. D_2O exchange of the amide proton at 7.0 ppm changes the multiplicity of the C_8 absorption to the expected doublet. The difference in chemical shift for amide protons in the isomeric acetamides may be due to the anisotropic effect of the phenyl ring in the β-amide proton.

The C_4' aromatic proton in the spectrum of the β-acetamide (6) was located at 7.4 ppm, slightly upfield ($\Delta\delta$= 0.20 ppm) from this pattern in the β-amine (5); probably because of the reduced basicity of the nitrogen. It is significant that the C_4 proton signal did not change from its position in the spectrum of the β-amine. This clearly suggests that the highfield position of this proton is possibly due to shielding by the aromatic ring rather than the nitrogen. All other

proton absorptions of the acetamides (6 & 7) maintain their position (± 0.05 ppm) compared with the amines.

Compounds (8-13 & 21) are additional C_8 diastereoisomeric amides whose PMR spectra show the general patterns just discussed. Chemical shift data from these spectra are included in Table 11. Of particular interest is the spectrum of the diacylated compound (21). The benzylic proton resonance of this compound at 6.04 ppm, is downfield ($\Delta\delta$ = -0.80 ppm) from that in the monoacylated derivative (9), because of the inductive effect of the extra acyl group. Interestingly the aromatic region in the diacylated compound, in contrast to the monoacylated derivative and the β-amine (5), was observed as an apparent singlet.

The PMR spectrum of the 2,8-bridged quaternary salt (20) shows several interesting features. N-methyl, C_1 bridgehead and C_3 methylene proton absorptions moved downfield in the cyclic quaternary salt as expected due to the strong deshielding influence of the cationic nitrogen. The large downfield shift of C_3 methylene protons compared with that of the N-methyl protons is somewhat surprising. A deshielding effect from the carbonyl group which is rigidly held in proximity to the C_3 protons by the ring system may be responsible for their unusual downfield shift. The upfield position of C_{12} methylene resonance (3.42 ppm) in the cyclic quaternary salt compared with its precursor, 8β-chloroacetamide (13), demonstrates the weak

inductive effect of a positive nitrogen compared to that of a chlorine atom. The absorption by the C_{12} methylene protons of 13 is at a lower field (4.16 ppm) compared with that of 8β-phenylacetamide (11) (3.47 ppm), indicating the difference in the deshielding effect between a chlorine atom and a phenyl ring.

Reduction of the α/β-amides with LAH gave the corresponding alkylamines (14-19). The PMR spectra of these amines were similar to those of α/β-amines (4,5).

The 8α-aminomethyl-6,7-benzomorphan (23) formed by reduction of the 8α-nitrile (22) was also investigated. The PMR of this compound revealed complex splitting patterns for the C_8, C_{10} and C_1 protons in the 2.6-3.2 ppm region which integrated for 4H. Because of the overlapping lines of these protons it was difficult to determine the chemical shift and coupling pattern of the individual resonances. Deuterium oxide exchange of the amine protons at 1.54 ppm reduced the multiplicity of this absorption. Careful examination of the spectrum revealed a single triplet at 2.95 ppm ($J \sim 4$Hz) which was assigned to the C_1 bridgehead proton. This assignment was confirmed by examining the spectra of the amides (24-27). Acylation of the 8α-aminomethyl derivative (23) produced a downfield shift of the C_{10} methylene protons and a benzylic proton as expected whereas the C_1 proton signal did not change from its position in the spectrum of the amine (23).

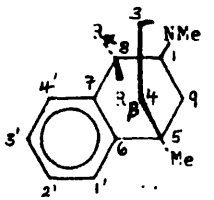
A molecule in which a methylene group is adjacent

to an asymmetric carbon centre forms an AB-system, a phenomenon which is well known[233]. The C_{10} methylenes of amides (24-27) have an adjacent asymmetric environment and thus give rise to an AB quartet, each component of which is coupled to the amide and benzylic proton (C_8-H) resulting in a complex methylene signal. Although D_2O exchange of the amide proton at 6.4 ppm reduces the multiplicity of this absorption, owing to resonance from the benzylic proton in this region, identification of the individual resonance lines was not possible.

The aromatic signal of the amides (24-27) is markedly broader than the corresponding amine (23). This change could be ascribed to the deshielding effect of the carbonyl group of the amide. The aromatic signal of 8α-alkylamines (28-30), formed by reduction of amides (24-26), is similar to that of 8α-aminomethyl-6,7-benzomorphan. This result lends support to the assumption that the difference in the aromatic protons chemical shift is due to the anisotropic effect of the carbonyl group.

Compounds (34-39) are additional examples of 8α-amino derivatives whose PMR spectra also show the general patterns discussed above. Chemical shift data are given in Table 11 and are consistent with the assigned 8α-configuration.

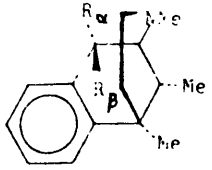
Table 11 100MHz ^{1}H NMR chemical shifts (δH) of 8-substituted Aminobenzomorphans.



Compound	No.	Aromatic-H C_1',C_2',C_3'	Aromatic-H C_4'	Alphatic-H C_1-H	Alphatic-H C_8-H_α	Alphatic-H C_8-H_β	Alphatic-H C_5-Me	Alphatic-H NMe	Other absorptions C_4-H	Other absorptions NH	Other absorptions
R_α,R_β=H 6,7-Benzomorphan (BM)	1	7.00-7.40		3.00	2.71	3.10	1.35	2.40			
R_α,R_β=O 8-Oxo BM	2	7.10-7.70	8.04	3.25			1.45	2.40			
R_α,R_β=N-OH 8-Oxime, $DMSO_4$	3	7.00-7.50	8.04	4.40			1.35	2.20			N-OH 11.53
R_α=NH_2,R_β=H α Amino BM	4	7.00-7.50		2.97		s 4.05	1.40	2.50		s 1.80	
R_α=H,R_β=NH_2 β Amino BM	5	7.00-7.40	7.58	3.00	d 4.00		1.33	2.62	0.90	s 2.04	
R_α=$NHCOCH_3$,R_β=H α Acetamido BM	6	7.00-7.50		3.07		d 5.20	1.40	2.56		d 5.9	CH_3CONH 1.92 s
R_α=H,R_β=$NHCOCH_3$ β Acetamido BM	7	7.10-7.30	7.40	3.00	dd 5.30		1.37	2.60	0.96	d 7.00	CH_3CONH 2.14 s
R_α=NHCO-c-C_3H_5,R_β=H α Cyclopropionamido BM	8	7.00-7.50		3.10		d 5.30	1.40	2.60		d 5.92	CO-c-C_3H_5 0.60-1.10
R_α=H,R_β=NHCO-c-C_3H_5 β Cyclopropionamido BM	9	7.10-7.30	7.40	3.00	dd 5.20		1.37	2.62		d 7.00	CO-c-C_3H_5 0.60-1.10

Compound	No.	Aromatic-H		Alphatic-H					Other absorptions			
		C_1',C_2',C_3'	C_4'	C_1-H	C_8-H_α	C_8-H_β	C_5-Me	NMe	C_4-H	NH		
R_α=$NHCOCH_2Ph$,R_β=H						d				d	$PhCH_2CO$	$PhCH_2CO$
α Phenylacetamido BM	10	7.00-7.50		3.05		5.20	1.36	2.60		5.72	3.50	7.20-7.40
R_α=H,R_β=$NHCOCH_2Ph$					dd					d	$PhCH_2CO$	$PhCH_2CO$
β Phenylacetamido BM	11	7.10-7.30		2.90	5.20		1.33	2.44	0.90	7.00	3.69	7.20-7.60
R_α=$NHCOCH_2Cl$,R_β=H						d				d	$ClCH_2CO$	
α Chloroacetamido BM	12	7.00-7.50		3.08		5.20	1.40	2.60		6.60	4.00	
R_α=H,R_β=$NHCOCH_2Cl$					dd					d	$ClCH_2CO$	
β Chloroacetamido BM	13	7.00-7.24	7.32	3.10	5.22		1.38	2.62	1.00	8.16	4.16	
R_α=$NHCH_2CH_3$,R_β=H						s					CH_3CH_2NH	CH_3CH_2NH
α Ethylamino BM	14	7.10-7.50		3.08		3.77	1.40	2.52			2.98 q	1.16 t
R_α=H,R_β=$NHCH_2CH_3$					d						CH_3CH_2NH	CH_3CH_2NH
β Ethylamino BM	15	7.00-7.40	7.74	3.17	3.74		1.35	2.62	0.90		2.92 q	1.20 t
R_α=$NHCH_2$-c-C_3H_5 ,R_β=H						s					CH_2	CH_2
α Cyclopropylmethylamino BM	16	7.10-7.50		3.05		3.80	1.40	2.50			2.68	0.00-1.20
R_α=H,R_β=$NHCH_2$-c-C_3H_5					d						CH_2	CH_2
β Cyclopropylmethylamino BM	17	7.00-7.40	7.76	3.13	3.75		1.33	2.60	0.90		2.68	0.00-1.2
R_α=$NHCH_2CH_2Ph$,R_β=H						s					$PhCH_2CH_2$	$PhCH_2CH_2$
α Phenylethylamino BM	18	7.00-7.50		3.08		3.76	1.37	2.49			3.00 m	7.10-7.50
R_α=H,R_β=$NHCH_2CH_2Ph$					d						$PhCH_2CH_2$	$PhCH_2CH_2$
β Phenylethylamino BM	19	7.00-7.40	7.70	3.16	3.73		1.32	2.55	0.90		3.00 m	7.10-7.40
2,8-bridged BM ($DMSO_4$)	20	7.10-7.30	7.68	4.32	5.16		1.47	3.32		d 9.84	$NHCOCH_2N^+$ 3.42	C_3 4.30
R_α=H,R_β=$N(CO\text{-}c\text{-}C_3H_5)_2$					d						$(CH_2\text{-}c\text{-}C_3H_5)_2$	
β Dicyclopropionamido BM	21	7.00-7.40		3.04	6.08		1.32	2.52			0.80-1.30	

Compound	No.	Aromatic-H		Alphatic-H				Other absorptions		
		C_1',C_2',C_3'	C_4'	C_1-H	C_8-H_α	C_8-H_β	C_5-Me	NMe	C_4-H	NH
R_α=CN, R_β=H					s					
α Cyano BM	22	7.00-7.50		3.42	4.14	1.38	2.40			
R_α=CH_2NH_2, R_β=H					C_8H-CH_2-NH				s	
α Aminomethyl BM	23	7.00-7.40		2.92	2.60-3.10	1.36	2.40		1.54	
R_α=$CH_2NHCOCH_3$, R_β=H										CH_3CONH
α Acetamidomethyl BM	24	7.00-7.60		2.98	3.08-3.80	1.38	2.37		6.44	2.03
R_α=CH_2NHCO-c-C_3H_5, R_β=H										CO-c-C_3H_5
α Cyclopropionamidomethyl BM	25	7.00-7.6		2.98	3.08-3.80	1.38	2.37		6.36	0.60-1.00
R_α=$CH_2NHCOPh$, R_β=H										$PhCH_2CO$ $PhCH_2CO$
α Phenylacetamidomethyl BM	26	7.00-7.60		2.76	2.92-3.60	1.33	2.2o		5.92	3.58 7.20-7.60
R_α=$CH_2NHCOCH_2Cl$, R_β=H										$COCH_2Cl$
α Chloroacetamidomethyl BM	27	7.00-7.50		2.95	3.08-3.80	1.40	2.37		6.34	4.07
R_α=$CH_2NHCH_2CH_3$, R_β=H										CH_3CH_2NH CH_3CH_2NH
α Ethylaminomethyl BM	28	7.00-7.40		2.80	2.60-3.30	1.38	2.40			2.60-2.80 1.12 t
R_α=CH_2NHCH_2-c-C_3H_5, R_β=H										CH_2-c-C_3H_5 CH_2-c-C_3H_5
α Cyclopropylmethylaminomethyl BM	29	7.00-7.40		2.80	2.60-3.30	1.39	2.43			2.54 0.00-1.10
R_α=$CH_2NHCH_2CH_2Ph$, R_β=H										$PhCH_2CH_2$ $PhCH_2CH_2$
α Phenylethylaminomethyl BM	30	7.00-7.40		2.80	2.60-3.30	1.4	2.37			2.60-3.00 7.10-7.50



Compound	No.	Aromatic-H C_1',C_2',C_3'	Aromatic-H C_4'	Alphatic-H C_1-H	Alphatic-H C_8-H_α	Alphatic-H C_8-H_β	C_5-Me	NMe	C_9-Me	NH	Other absorptions	
R_α,R_β=H					m							
6,7-Benzomorphan	31	7.00-7.30		2.38-3.20			1.35	2.35	0.85			
R_α,R_β=O												
8-Oxo BM	32	7.20-7.70	8.00	3.00			1.40	2.35	0.85			
R_α,R_β=N-OH											N-OH	
8-Oxime BM	33	7.00-7.40	8.00	4.24			1.35	2.28	0.72		11.0	
R_α=NH_2,R_β=H					s							
α Amino BM	34	7.00-7.60		2.88	3.96		1.35	2.45	0.96	1.90		
R_α=$NHCOCH_3$,R_β=H					d						CH_3CONH	
α Acetamido BM	35	7.00-7.40		2.95	5.25		1.40	2.60	0.92	5.80	2.00	
R_α=$NHCO\text{-}c\text{-}C_3H_5$,$R_\beta$=H					d						$CO\text{-}c\text{-}C_3H_5$	
α Cyclopropionamido BM	36	7.00-7.40		2.96	5.28		1.40	2.60	0.90	5.85	0.60-1.10	
R_α=$NHCOCH_2Ph$,R_β=H					d						$PhCH_2CO$	$PhCH_2CO$
α Phenylacetamido BM	37	7.00-7.50		2.80	5.20		1.30	2.60	0.90		3.60	7.00-7.50
R_α=$NHCH_2CH_3$,R_β=H					s						CH_3CH_2NH	CH_3CH_2NH
α Ethylamino BM	38	7.00-7.30	7.40	2.80	3.60		1.30	2.40	0.84		1.05 t	2.60-3.10 q
R_α=$NHCH_2\text{-}c\text{-}C_3H_5$,$R_\beta$=H					s						$CH_2\text{-}c\text{-}C_3H_5$	
α Cyclopropylmethylamino BM	39	7.00-7.30	7.40	2.80	3.60		1.32	2.40	0.90		0.00-0.60 m	

6.1 ^{13}C NMR studies.

6.1.1 Introduction.

Carbon-13-NMR spectra used in combination with ^{1}H spectra give unparalleled insight into the details of organic molecular structures. Application of ^{13}C NMR spectroscopy to the determination of structure and stereochemical features of molecules is well established and is routinely exploited. The tremendous strides taken in the advancement of ^{13}C NMR techniques and instrumentation have rendered ^{13}C spectroscopy a routine chemical tool offering powerful new approaches to the solution of a wide range of problems[234-237].

Carbon resonances of organic compounds are found over a chemical range of 220 ppm compared with the $<$20 ppm range for proton nuclei. The large chemical shift range enormously increases the effective resolution. Since ^{13}C spectra are routinely recorded with complete proton decoupling, they consist entirely of singlet signals and frequently separate resolved signals are seen for each individual carbon atom in molecules. Additional advantages of carbon-13-NMR is that it allows direct observation of molecular backbones and of quaternary carbon containing functional groups. The dependence of chemical shifts on molecular geometry and substitution makes ^{13}C NMR spectroscopy a powerful structural and stereochemical tool[237].

In general, trends of ^{13}C shielding are similar to these found for protons, with Sp^3 hybridized carbon

atoms absorbing at highfield, Sp^2 carbon at lower field and Sp hybridized carbon at intermediate field. The effects of electronegative shift to lower field follow the expected pattern with increasing shift to lower field caused by more polar groups. For example, the carbonyl carbons appear in the range of 160-220 ppm. In an unsaturated system, substituents can affect the shielding of remote carbon centres by withdrawing or donating electrons. Increasing electron density generally shifts the resonances towards higher field[237].

The striking feature of ^{13}C shielding data is the remarkable consistency of substituent effects in closely related systems, with the general finding that a simple additivity relation correlates the shielding data within various families of compounds with good precision. An early example was described by Grant and Paul[238] for acyclic hydrocarbons.

The effect of a substituent in ^{13}C shift is not confined to the nearest atom as in proton chemical shift but $\beta, \gamma, \delta, \varepsilon$, positions are also affected. In general a substituent in the α- and β positions deshields the carbon nucleus but one in the γ position is shielding In acyclic alkanes the effect of substituents in the γ or further positions are very small but in cyclic compounds these long range effects may be quite significant.

The γ effect is of particular interest in conformational studies as it is subjective to relative

stereochemistry. A semitheoretical rationalization of the origin of the γ effect was presented by Grant and Cheney[239] in terms of a model for non-bonded steric interaction between closely neighbouring atoms in hydrocarbons. However it is now recognized that this cannot be the sole source of this effect because such shielding is often observed even when no such interaction is possible. A more compelling argument against a steric origin for these effects is the deshielding arising from a geometrically proximate δ-substituent. Although the mechanistic origin of this effect remains unclear, it is of great value for stereochemical studies[234-237].

A wide range of techniques is available for the assignment of ^{13}C NMR signals. Most widely used are those based on particular types of ^{1}H decoupling. ^{13}C resonances in an off resonance ^{1}H decoupling experiment show first order multiplicity and thus primary, secondary, tertiary and quaternary carbon atoms can be distinguished. Other decoupling experiments employed are selective ^{1}H decoupling and off-resonance decoupling with variable-frequency off set[236,237].

Among chemical methods employed for the assignment of ^{13}C NMR signals, there are shifts induced by the addition of shift reagents, by changing the pH of the solution causing protonation or deprotonation or by solvent effects. In addition chemical modification such as simple derivatization or selective deuterium incorporation are also of diagnostic value. Finally, in the case of complicated structures such as those

of natural products, relaxation times (T_1) measurements are increasingly used to assign different ^{13}C resonances.

6.1.2 ^{13}C NMR spectral characteristics and stereochemical investigation.

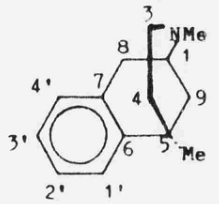
The ^{13}C NMR chemical shifts of a series of 8-substituted-6,7-benzomorphans prepared are listed in Table 12. The structural and stereochemical information from the ^{1}H NMR studies described above was considered along with the application of established chemical shift parameters[235-36], off-resonance decoupled (OFR) spectra, and comparisons with structurally related compounds to arrive at the complete ^{13}C NMR chemical shift assignments of these compounds. Carbon-13-NMR studies of morphine alkaloids[240-241] are of special relevance in this respect.

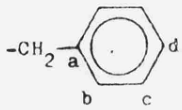
The 2,5-dimethyl-6,7-benzomorphan (1) is employed as the parent member and model for the series because the stereochemistry of derivatives related to it is well established[109,228]. The unprotonated aromatic carbons, C_6 and C_7 were easily differentiated from other aromatic carbons by their low position and the fact that they appeared as a singlet in OFR spectra. They were also, as expected, of reduced intensity because of their longer relaxation times (T_1). The C_6 singlet was shifted downfield 7 ppm compared with the C_7 due to the strong deshielding imposed on it by the

attached quaternary centre; C_7 is bonded to a primary centre. The C_7 signal is also broader than that of C_6 owing to long range coupling to the methylene protons of C_8. The ^{13}C chemical shift values for the other aromatic carbons were obtained from the substituent additivity rule for a benzene ring and by comparing the shifts of tetralin[235]. The highfield aromatic methine signal was assigned to C_1' as it is shielded by interaction with the C_5-methyl. Carbon$_4$' doublet appeared at lower field compared with C_2' and C_3' presumably due to an ortho effect from the C_7 substituent. It was not possible to assign the two lines arising from C_2' and C_3' as they are separated by only 0.3 ppm, a value which barely exceeds the experimental error.

The N-methyl is assigned to the lower field quartet of the OFR spectrum and is easily distinguished from the C_5-methyl (q) not attached to a heteroatom. Carbon$_8$ methylene is at unusually highfield in accord with its antiperiplanar relationship to the nitrogen lone orbital. Lone-pair shielding of this type has been discussed by Eliel and Pietrusiewicz[242] in the case of some N,2α- and N,2β-dimethyl decahydroquinolines (198) and the phenomenon is also evident in data on the mobile systems N,t-2,6-, N,t-2,3- and N,t-2,4-trimethylpiperidine[242] where axial contributions move the C_2' chemical shifts upfield relative to the corresponding shifts of the eq-2-Me analogues. Other examples are provided by the 2-methyl-4-phenylpiperidines[243].

Table 12 ^{13}C NMR chemical shifts (δC) of 8-substituted Aminobenzomorphans. Compounds no's 1-39 refer to those in Table 11.





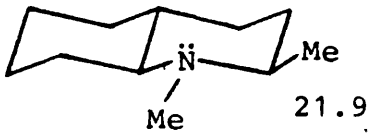
	Aromatic Carbons					Aliphatic Carbons									
No.	C_1'	C_2'	C_3'	C_4'	C_6	C_7	C_1	NMe	C_3	C_4	C_5	C_5-Me	C_8	C_9	Other Carbons
1	124.3	125.3	125.5	127.3	143.4	136.8	51.1	42.5	47.1	40.6	31.1	27.8	27.2	39.8	
2	125.3	134.0	125.7	126.4	148.8	134.0	63.4	43.1	47.1	40.8	32.5	27.7	194.4	39.6	
3	121.6	129.6	125.8	125.8	143.7	133.0	49.0	43.8	47.7	40.5	31.9	27.9	150.7	39.5	
4	124.8	128.5	126.3	127.4	144.0	140.3	62.3	42.8	47.3	40.6	32.3	27.8	46.0	35.5	
5	123.8	126.2	126.0	126.2	142.2	142.7	58.8	42.8	45.9	34.0	33.5	28.6	52.9	34.5	
6	124.9	129.9	126.4	129.1	144.4	137.7	59.3	42.7	47.5	40.7	32.1	27.9	44.6	36.8	CO - CH_3 168.2 23.2
7	124.3	127.3	126.6	127.2	142.5	139.0	57.0	42.8	46.3	34.6	33.4	28.7	50.0	33.7	CO - CH_3 170.1 23.7

	Aromatic Carbons						Aliphatic Carbons								
No.	C_1'	C_2'	C_3'	C_4'	C_6	C_7	C_1	NMe	C_3	C_4	C_5	C_5-Me	C_8	C_9	Other Carbons
8	124.9	129.1	126.4	128.1	144.3	137.5	59.1	42.7	47.4	40.6	32.0	27.9	44.4	36.7	CO - c-C_3H_5 171.9 14.7, 7.0
9	124.2	129.2	126.6	127.2	142.6	139.0	57.7	42.8	46.2	34.4	33.4	28.8	50.2	35.0	CO - c-C_3H_5 173.8 14.7, 6.8
10	124.8	129.1	126.9	128.1	144.3	137.0	59.1	42.7	47.4	40.5	32.0	27.9	44.4	36.6	CO - CH_2 - Ph 169.4 43.8 a. 135.1 b. 129.2 c. 128.9 d. 127.2
11	124.2	127.2	126.7	127.2	142.6	139.0	57.8	42.8	46.2	34.1	33.4	28.7	50.2	35.0	CO - CH_2 - Ph 171.7 44.3 a. 135.5 b. 129.4 c. 128.8 d. 127.1
12	125.1	129.1	126.7	128.5	144.5	136.6	59.2	42.7	47.5	40.7	32.2	27.9	45.0	36.9	CO - CH_2Cl 164.5 42.7
13	124.4	127.5	126.7	127.1	142.7	138.3	57.0	43.0	46.3	34.1	33.4	28.7	50.7	35.0	CO - CH_2Cl 166.8 43.1
14	124.5	128.4	126.1	127.3	143.7	140.5	57.8	42.5	47.5	40.5	32.1	27.8	52.2	36.0	$NHCH_2$ - CH_3 42.8 15.9
15	123.9	127.6	126.2	126.4	142.5	141.8	54.7	42.8	46.5	34.2	33.6	29.0	59.7	34.7	$NHCH_2$ - CH_3 42.9 16.0
16	124.6	128.4	126.1	127.3	143.7	140.5	57.9	42.5	47.5	40.5	32.1	27.8	52.1	36.0	$NHCH_2$ -c-C_3H_5 54.0 11.8, 3.2
17	123.9	127.7	126.2	126.4	142.5	141.9	54.6	42.9	46.4	34.2	33.6	29.0	59.6	34.7	$NHCH_2$ -c-C_3H_5 54.0 12.0, 3.4
18	124.5	128.5	126.1	127.3	143.8	140.3	57.8	42.5	47.5	40.5	32.1	27.9	52.5	36.0	$NHCH_2$ - CH_2 - Ph 50.2 37.1 a. 140.2 b. 128.8 c. 128.5 d. 126.1
19	124.0	127.6	126.0	126.5	142.6	141.6	54.7	42.9	46.5	34.2	33.6	29.0	60.1	34.8	$NHCH_2$ - CH_2 - Ph 50.3 37.5 a. 141.0 b. 128.9 c. 128.3 d. 126.5

	Aromatic Carbons					Aliphatic Carbons									
No.	C_1'	C_2'	C_3'	C_4'	C_6	C_7	C_1	NMe	C_3	C_4	C_5	C_5-Me	C_8	C_9	Other Carbons
20	124.1	128.0	126.4	127.0	140.5	135.2	59.3	49.4	59.0	31.0	33.2	25.6	49.8	30.3	CO - CH_2N^+ 160.4 61.8
21	124.9	126.7	125.4	126.5	141.9	136.4	57.9	43.8	45.4	34.9	33.4	29.0	60.7	35.5	CO - c-C_3H_5 176.7, 176.1 22.5, 22.0, 11.4, 11.0
22	125.5	128.6	126.8	128.6	143.5	130.7	57.7	42.7	47.0	40.3	31.7	27.7	28.2	37.4	CN 121.3
23	124.6	128.0	125.8	126.4	144.2	139.3	56.1	42.3	47.6	40.8	32.2	27.9	39.0	36.7	C_{10}-NH CH_2NH_2 49.0 49.0
24	124.7	128.2	126.0	126.8	144.2	138.4	56.4	42.4	47.5	40.9	32.2	27.9	35.8	36.5	46.4	CH_2NH - CO - CH_3 46.4 170.2 23.2
25	124.2	128.3	126.0	126.8	144.3	138.5	56.5	42.3	46.7	41.0	32.3	27.9	36.0	36.5	46.5	CH_2NH - CO -c-C_3H_5 46.5 173.7 14.7, 6.8
26	124.7	128.2	126.0	126.8	144.2	138.1	56.5	42.3	47.5	41.0	32.2	27.9	35.5	36.5	46.2	CH_2NH - CO - CH_2 - Ph a. 135.1 b. 129.4 46.2 170.9 44.1 c. 129.2 d. 127.5
27	124.9	128.2	126.2	127.1	144.4	137.9	56.8	42.8	47.6	41.0	32.3	27.9	35.8	36.6	46.4	CH_2NH - CO - CH_2Cl 46.4 166.1 42.4
28	124.4	127.9	125.6	126.3	144.2	139.9	56.6	42.3	47.6	41.0	32.2	28.1	35.9	36.7	56.9	CH_2NH - CH_2 - CH_3 56.9 44.1 15.3
29	124.6	128.1	125.7	126.3	144.3	139.9	56.5	42.2	47.7	41.1	32.2	27.9	35.8	36.7	56.9	CH_2NH - CH_2 - c-C_3H_5 56.9 54.9 11.4, 3.4
30	124.6	128.1	125.8	126.4	144.3	139.7	56.5	42.3	47.6	41.0	32.2	27.9	35.7	36.6	56.8	CH_2NH - CH_2 - CH_2 - Ph a. 140.3 b. 128.8 56.8 50.9 29.7 c. 128.5 d. 126.2

	Aromatic Carbons						Aliphatic Carbons									
No.	C_1'	C_2'	C_3'	C_4'	C_6	C_7	C_1	NMe	C_3	C_4	C_5	C_5-Me	C_8	C_9	C_9-Me	Other Carbons
31	124.8	125.1	125.5	127.3	141.3	136.6	59.5	42.7	47.5	42.7	35.9	25.5	23.6	42.1	14.1	
32	126.3	133.8	126.8	126.2	145.2	134.5	69.2	43.1	47.6	42.6	36.1	26.0	194.8	42.7	15.0	
34	125.4	127.6	126.1	127.2	141.6	140.2	68.0	42.7	47.2	42.4	36.2	25.8	44.6	41.2	15.3	
35	125.8	128.2	126.3	128.0	141.6	137.1	65.3	42.4	47.4	42.4	36.1	25.9	43.0	41.2	15.2	CO - CH_3 168.4 23.4
36	125.8	128.1	126.3	128.1	141.6	137.2	65.2	42.4	47.4	42.4	36.1	25.7	43.0	41.2	15.3	CO -c-C_3H_5 172.0 14.8, 7.0
37	125.8	128.1	126.3	128.1	141.6	137.2	65.3	42.5	47.4	42.4	36.1	25.1	43.0	41.2	15.2	CO - CH_2 - Ph 170.1 43.8
38	125.4	128.3	126.0	127.3	141.1	140.8	63.0	42.7	47.6	42.5	36.2	26.0	50.7	41.8	15.3	$NHCH_2$ - CH_3 43.1 15.8
39	125.3	128.2	126.0	127.2	141.0	140.7	62.7	42.5	47.6	42.6	36.1	26.0	50.8	41.7	15.3	$NHCH_2$ -c-C_3H_5 54.0 11.8, 3.4

It is of interest that a similar upfield shift of an antiperiplanar lone pair has been known in proton NMR spectroscopy[244,245].



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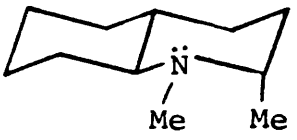


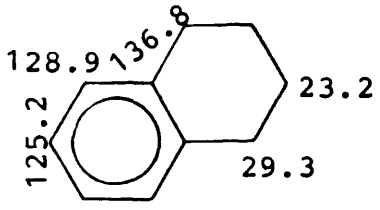
9.1

(198)

Carbon$_1$ (d) and carbon$_3$ (t) resonances were downfield due to nitrogen substitution and easily distinguished from the carbons not attached to a heteroatom. Carbon$_3$ was distinguished by its consistency throughout the series. The small chemical shifts difference between the two remaining methylenes (C_4 & C_9) made completely unambiguous assignment difficult. However differentiation of the C_4 and C_9 triplets was accomplished by comparing 6,7-benzomorphan to 8α-amino-6,7-benzomorphan (4). The amino group should shift the C_9 resonance upfield due to its γ effect while that of C_4 should remain unchanged. This type of shift was noted in going from 6,7-benzomorphan (1) to 8α-aminobenzomorphan (4). The C_5 singlet was, as expected, of reduced intensity compared to other carbon signals and was easily identified by its consistency throughout the series.

Introduction of an electronegative oxygen at C_8

appreciably changes the local charge density of the adjacent carbon atoms. The carbon$_1$ shifted downfield $\sim$ 12.0 ppm in the 8-oxo compound (2) compared with 6,7-benzomorphan (1). This downfield shift is similar to that noted at the α-carbon in cyclohexanone (13.6 ppm) compared with cyclohexane[246]. The carbonyl substituent caused a large downfield shift of the C_2' and C_6 resonance and an upfield shift of C_7 and C_4'. Carbon shift analyses of these aromatic carbons were made on the basis of the shifts of α-tetralone (200) compared with those of tetralin (199)[235].



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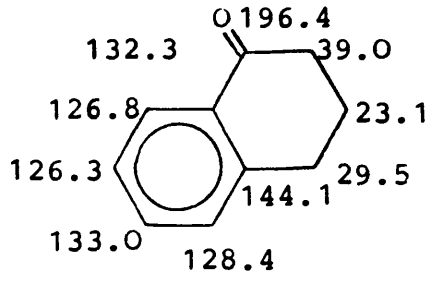


(200)

The assignment of the carbonyl carbon, C_8, is straightforward since it appears as a singlet at the lowest field position. The carbonyl shift (194 ppm) is similar to that noted for ortho substituted acetophenones. It is known that an important factor contributing to the carbonyl chemical shift is conjugation[234]. The carbonyl carbon of a conjugated system appears at a significantly higher field compared with an analogous saturated derivative. This

shielding effect indicates that the electron density about a conjugated carbonyl carbon nucleus may be substantially greater than that about a saturated carbonyl carbon nucleus. Studies of proton spectra also indicate a greater electron density at the conjugated carbonyl carbon. If the conjugated interaction of the aromatic nucleus with the carbonyl group is diminished, the carbonyl peak appears towards lower field relative to an electronically similar, but unhindered derivative[247].

The carbon$_8$ resonance of oxime (3) appeared in the region 150 ppm; it is some 50 ppm higher relative to corresponding carbonyl resonance. The highfield chemical shift of C_1 carbon (49.02 ppm) suggested the N-OH group is facing the C_1 group[236].

The ^{13}C NMR spectra of 8α- and 8β-aminobenzomorphan (4 & 5) showed several interesting differences and demonstrated the effect of substituent geometry on chemical shifts. The C_8 of α/β-amines was easily identified by examining the spectra of the amines and the unsubstituted benzomorphan (1). The C_8 triplet of the benzomorphan was replaced by a downfield doublet in the spectra of amines (4 & 5). This shift is due to a change in the electron density caused by the electronegative amino group. This substituent also caused a downfield shift of β-carbon atoms, C_1 and C_7. Carbon$_9$ triplet appeared at higher field than that of 6,7-benzomorphan (1) owing to the γ effect of the amino substituent. Eliel *et al*[248] have discussed shielding

influences of nitrogen when gauche or antiperiplanar to a γ-carbon, and have concluded that both influences generally move the carbon resonance upfield. The origin of this effect is not clear but it has been postulated that it is due in the main not to the substituent but to the removal of the hydrogen atom it replaces[249].

Comparison of α- and β-amine (4 & 5) spectra shows that the α-amino isomer has a smaller downfield shift at C_8 and C_7 but a larger downfield β effect at C_1. The C_8 in the α-amine appeared at 46.00 ppm, upfield by 7 ppm from that in the β-amine (5). The α-C_7 singlet is also ~2.0 ppm upfield from its position in the β-amine spectrum. The α-C_1 doublet at 62.3 ppm is 3.5 ppm downfield relative to the β-amine.

There were significant differences in the chemical shifts for C_9, C_3 and C_5; these carbon resonances are upfield in the β-amine (5) compared to those in the α-amine (4). The β-amino substituent causes upfield shifts (~1 ppm) of C_3 and C_5 even though the groups are well separated. The other main spectral difference between the α- and β-amino isomers was found in the shift of the C_4. The α-C_4 resonance is close to that of C_4 in the unsubstituted benzomorphan (1) while in the β-amino isomer it is shifted upfield ~7.ppm. These differences in shifts are not fully understood at present but are probably due, in part, to differences in conformation of the isomers. The amino group in the β-amine (5) is orientated to the more hindered position.

The severe nonbonded repulsion between the β-amino nitrogen and the ring nitrogen present when the piperidine ring moiety is in the chair form may be substantially relieved in the non-chair form. An unusually highfield C_4 proton shift (near 0.9 ppm) of the β-amine also suggests some deformation of the ring C.

The epimeric acetamides (6 & 7) synthesized from the α- and β-amines respectively were also studied. Carbon-13-NMR spectra of these compounds showed the general patterns discussed for the isomeric amines. Introduction of an acetyl group modifies the shift of the C_8 as well as those of its immediate neighbours C_1 and C_7. The C_8, C_7 and C_1 resonances of the amides were shifted upfield relative to their position in the amines. These upfield shifts are as expected with change in the electronegativity of the nitrogen and β and γ effects from the acetyl groups. The acetyl group produces a larger chemical shift on C_7 and C_8 but a smaller shift on C_1 in the β-acetamide (7) compared to α-acetamide (6). An explanation for these differential effects is not readily apparent. The chemical shift of all other carbons of the amides were similar,,within a narrow range of ±0.5 ppm, to the corresponding amines.

The acetamides' (6 & 7) carbonyl carbons were easily identified as the lowest field resonances in the spectra. The carbonyl of β-acetamide at 170.7 was slightly lowfield from that of α-acetamide. The acetyl

methyl gave a quartet in OFS spectra which appeared in the region (23.0 ppm) expected for a methyl next to a carbonyl group.

Compounds (8-13) are additional examples of isomeric amides whose NMR spectra were entirely analogous to those just discussed. A comparison of shifts for the acetyl methyl of 8α-acetamide with the corresponding 8α-chloroacetamide methylene shows the effect of replacement of hydrogen by a chlorine of ~20 ppm is somewhat less than that observed in other systems for a similar substitution (entry 6 and 12). For example, chlorine substitution in aliphatic hydrocarbons deshields an α-C by ~30 ppm[234]. It would appear that the carbonyl group interacts with the chlorine in some way to produce an effect which opposes the chlorine effect. Phenyl ring substitution at the acetyl methyl of acetamide deshields the carbon by an essentially identical value, ~20 ppm (entry 6 and 10). This downfield shift is similar to that noted at the α-carbon in aliphatic compounds[234,235].

The carbonyl chemical shift for α-cyclopropionamide, α-phenylacetamide and α-chloroacetamide (8,10 & 12) were at 171.9, 169.4 and 164.5 ppm respectively. The carbonyl carbon of chloroacetamide (12) absorbed furthest upfield of all carbonyls. Carbonyl atoms of β-amides (7,9 &11) followed a similar pattern although these carbonyls appeared at a slightly lower field that those of the corresponding α-amides.

The chemical shift for the cyclopropyl group in α/β-cyclopropionamide (8 & 9) appeared at a very high-field. The cyclopropyl methine (d) came at ~15 ppm and cyclopropyl methylene (t) appeared at ~7 ppm. The assignments for carbons of the N-phenylacetyl group of α/β-phenylacetamido derivatives were made with the aid of chemical shift parameters of monosubstituted benzene[234,236]. For a monosubstituted phenyl group; the carbon "a" appeared to be the most deshielded whereas the para carbon "d" was slightly shielded. Carbons at the ortho position (Cb) occurred upfield of those at meta (Cc).

The ^{13}C NMR spectrum of 8β-dicyclopropionamide (21) was of particular interest. Introduction of a second acyl group has a striking effect on the benzylic carbon (C_8). This carbon signal was located at 60.7 ppm, downfield ($\Delta\delta$ = 10.5 ppm) from its position in the spectrum of monoacylated derivative (9). The cyclopropyl groups in the diacylated compound (21) also appeared at a lower field relative to the monoacylated derivative (9). The cyclopropyl methylene signal was not well resolved and appeared at ~11.0 ppm as a broad peak. The cyclopropyl methine appeared at ~21-23 ppm as two separate doublets. The spectrum showed two separate carbonyl singlets at 178.6 and 176.0 ppm. Environmental features may be responsible for the slight differences in the carbonyl absorption.

Reduction of α/β-acetamides (6 & 7) resulted in

a large downfield shift of C_8 ($\Delta\delta$= 6.8 ppm) because of the larger β effect of the alkyl substituents. The γ effect of a N-ethyl group, as expected, shifted C_1 to a higher field. In contrast, aromatic C_7 which is also γ to the N-alkyl, was shifted downfield ~3 ppm relative to the amides (6 & 7), but surprisingly its chemical shift differs little from that of a primary amine (4 or 5). The magnitude of the change in the chemical shift of C_8, C_1 and C_7 were similar in both α- and β-alkylamines (14 & 15).

A comparison of the shifts for isomeric primary amines (4 & 5) with the corresponding secondary alkylamines (14 & 15) shows the effect of replacement of the proton in nitrogen with an alkyl group. Introduction of an alkyl group on the nitrogen produces β, γ and δ effects on the carbons respectively of very similar magnitude to those observed for alkyl substitution in cyclohexane[234-240,246]. The amide carbonyl singlet on reduction of the amide was replaced by a new triplet which appeared in the expected lowfield region for a methylene next to a nitrogen. The methyl of the N-ethyl group in ethylamines (14 & 15) appeared at 16.0 ppm.

Compounds (16-19) are additional derivatives in which the amino group bears an alkyl substituent; these spectra were similar to the spectra of α- and β-ethylamino-benzomorphans (14 & 15). The chemical shifts of C_8, C_7 and C_1 were affected very slightly by larger N-alkyl substituents in these compounds. The cyclo-

propyl group in the alkylamines (16 & 17) was shifted upfield owing to the expected smaller α and β effect of the methylene function compared to the carbonyl group in the amides (8 & 9). In the phenylethylamino-6,7-benzomorphans (18 & 19), methylene groups α and β to the 2^{o} amino function ($PhCH_2$ and $PhCH_2CH_2$) appeared at 37.1 ppm and 50.2 ppm respectively.

The general ^{13}C NMR features of the 8α-nitrile (22) synthesized from 8-oxobenzomorphan (2), are close to that of 8α-aminobenzomorphan (4). The substituent effects of the cyano group parallel that of the amino group, although the effects are smaller. The polar cyano group would be expected to give a larger α effect if inductive polarization dominates and it is clear that other factors contribute substantially in the case of the triple bonded grouping. The magnetic anisotropy of the nitrile triple bond has, on occasion, been invoked to explain its very much reduced deshielding influence[234-236].

The C_8 and C_1 resonances were at a lower field in the spectrum compared with those of the benzomorphan (1) as anticipated from the α and β deshielding influences of the cyano substituent. The C_9 triplet was shifted upfield due the γ effect of the cyano group. The aromatic C_7, which is β to the cyano moiety, exhibited a somewhat surprising upfield shift of 5.4 ppm relative to 6,7-benzomorphan. This behaviour is opposite to that found for the aliphatic C_1, which

is also β to the cyano substituent. Replacement of the methyl hydrogen of toluene by a nitrile group is reported to produce a similar upfield β effect on the aromatic carbon. The nitrile carbon gave a singlet which appeared in the region expected for the carbon multiply bonded to nitrogen (121.4 ppm). The shielding for most of the remaining carbons was relatively little affected by the cyano group.

The spectrum of 8α-aminomethyl-6,7-benzomorphan (23) obtained by reduction of the nitrile (22) showed general characteristics similar to that of the nitrile. The chemical shift of C_8 was lowfield 12.0 ppm relative to the nitrile owing to the α and β effect of the aminomethyl substituent. Aromatic C_7 was shifted downfield (8.6 ppm) as expected with the removal of shielding β effect of the cyano group. In contrast, C_1 was shifted upfield relative to its position in the nitrile. The downfield shift due to the β effect from the methylene (C_{10}) must be offset by a larger shielding influence of the nitrogen. Shifts of other carbon atoms further removed from the site of substitution were small.

The general trends exhibited by the acyl and alkyl substituent effects in the 8α-aminobenzomorphan were also observed in the spectra of a corresponding series of 8α-aminomethyl-6,7-benzomorphans (24-30) and 8α-amino-2,5,9-trimethyl-6,7-benzomorphans (34-39).

CHAPTER SEVEN

EXPERIMENTAL

CHAPTER SEVEN

Experimental

Analysis of compounds.

Infra-red spectra were recorded on a Pye Unicam SP.200 instrument and were obtained on liquid films or nujol mulls for solids.

^{1}H NMR spectra were recorded on a J.E.O.L. PS. 100 instrument operating at 100 MHz and 2.349 Tesla, or a Varian A60, 60 MHz spectrometer. PMR data are quoted to two decimal places unless the last number is zero.

^{13}C NMR spectra were recorded on a J.E.O.L. FX 90Q Fourier Transform NMR spectrometer operating at 22.9 MHz. TMS was used as internal standard.

Mass spectra were obtained on an AEI MS 50 mass spectrometer at Reckitt and Colman.

Elemental analysis were carried out at the micro-analytical laboratories in Reckitt and Colman (Hull). and London University.

Melting points were recorded on a Townson and Mercer apparatus. All melting points are uncorrected.

Thin layer chromatography (TLC) was carried out on silica gel (60) plates. Unless otherwise specified the solvent system employed for elution was methanol: dichloromethane:acetic acid (12:4:1). The plates were developed by immersion in an atmosphere saturated with iodine vapour for a few minutes.

Small-scale distillations were carried out with a

Kugelaohr microdistillation apparatus.

Light petroleum-ether had bp. 60-80^{o} unless stated otherwise.

In mass spectra the sign $\div \equiv$ minus.

7.0 2,5-Dimethyl-6,7-benzomorphan (40), 2'hydroxy-2,5-dimethyl-6,7-benzomorphan (111) and 2,5,9-trimethyl-6,7-benzomorphan (99).

These compounds were prepared according to the method of May[93]. Thus 2'hydroxy-2,5-dimethyl-6,7-benzomorphan (111) and the non-phenolic 2,5-dimethyl-6,7-benzomorphan (40) were synthesized in a three step process from 4-picoline methiodide and p-methoxybenzylmagnesium chloride, and 4-picoline and benzylmagnesium chloride, respectively. 2,5,9-Trimethyl-6,7-benzomorphan (99) was obtained from 3,4-lutidine methiodide and benzylmagnesium chloride.

2,5-dimethyl-6,7-benzomorphan·HCl mp 193-195°(from ethanol-ether). (Lit. mp 193-195°).

^{1}H nmr δ_{CDCl_3},base 1.35(3H,s,C_5-Me), 2.36(3H,s,NMe), 2.5-2.75(1H,m,$\underline{H}_{8\alpha}$), 3.0-3.3(2H,m, $\underline{H}_{8\beta}$ + $\underline{H}_1$), 7.0-7.4(4H,m,Ar-$\underline{H}$).

2'hydroxy-2,5-dimethyl-6,7-benzomorphan. mp 208-211° (from acetone). (Lit. mp 209-214°).

^{1}H nmr δ_{CDCl_3} 1.32(3H,s,C_5Me), 2.40(3H,s,NMe), 2.7-3.4(3H,m,H_1 + H_8), 6.5-7.0(5H, m,Ar-$\underline{H}$ + O$\underline{H}$, exchangeable).

2,5,9α-trimethyl-6,7-benzomorphan·HCl mp 203-204°
(from ethanol-ether). (Lit. mp 203-205°).

^{1}H nmr δ_{CDCl_3},base 0.85(3H,d,C_9-Me), 1.35(3H,s,C_5-Me), 2.35(3H,s,NMe), 2.5-3.2(3H,m,H_8 + H_1), 7.0-7.3(4H,m,Ar-H).

7.1 KETONES

7.1.1 2,5-Dimethyl-8-oxo-6,7-benzomorphan (100).

A 10% solution of chromium trioxide was prepared by dissolving chromium trioxide (21g) in acetic acid (190ml) and water 10ml). The chromium trioxide solution (80ml, 84mM) was added dropwise to a vigorously stirred mixture of 2,5-dimethyl-6,7-benzomorphan (5g, 25mM) in acetic acid (300ml). After addition was completed, the reaction mixture was stirred at room temperature for additional 20 hours. The solution was then poured into ice cold water, cautiously basified with ammonia solution and extracted with ether (4 x 100ml). The combined ethereal layers were extracted three times with 2N hydrochloric acid (100ml) and basified with ammonia solution. The liberated base was dried in ether. Removal of ether under reduced pressure afforded a dark brown oil, to which was added petroleum ether (~100ml). The insoluble material was separated and dissolved in ether to give, after cooling, 2,5-dimethyl-3,4,8-trioxo-6,7-benzomorphan (12%). Evaporation of the petroleum ether left a yellow oil which was chromatographed on silica. Methanol:dichloro-

methane:acetic acid (12:4:1) eluted two components which were identified as unreacted starting material (9.0%) and 2,5-dimethyl-8-oxo-6,7-benzomorphan (68%).

2,5-dimethyl-8-oxo-6,7-benzomorphan, mp 55-56° (from petroleum ether bp. 30-40°). (Lit. 54-57°).

ν_{max} 1680cm^{-1} ($CO_{str.}$)

^{1}H nmr δ_{CDCl_3} 1.45(3H,s,C_5-Me), 2.4(3H,s,NMe), 3.25(1H,t,C_1-H), 7.2-7.65(3H,m,Ar-H), 8.04(1H,m,C_4'-H).

Mass Spec. M/Z 215(M^+), 200($M^+ \div C_5$-Me), 172($M^+ \div C_5$-Me$\div$CO), 57(MeN$^{\cdot+}$⟨) base peak.

Elemental analysis:

Found C, 78.1 ; H, 8.0 ; N, 6.4%

$C_{14}H_{17}NO$ requires C, 78.1 ; H, 8.0 ; N, 6.5%

2,5-dimethyl-3,4,8-trioxo-6,7-benzomorphan.

ν_{max} 1730cm^{-1}, 1680cm^{-1}.

^{1}H nmr δ_{CDCl_3} 1.8(3H,s,C_5-Me), 2.64(2H,d,C_9-H), 3.08(3H,s,NMe), 7.2-7.64(3H,m,Ar-H), 8.04(1H,m,C_4'-H).

Mass Spec. M/Z 243(M^+).

7.1.2 2,5,9-Trimethyl-8-oxo-6,7-benzomorphan (115).

2,5,9-Trimethyl-6,7-benzomorphan was oxidized with chromic acid in the same manner as described in section 7.1.1 to give 2,5,9-trimethyl-8-oxo-6,7-benzomorphan (46%) and 2,5,9-trimethyl-3,4,8-trioxo-6,7-benzomorphan (18%).

2,5,9-trimethyl-8-oxo-6,7-benzomorphan. mp 64-66° (from petroleum ether bp. 30-40°).

ν_{max} 1670cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} 0.85(3H,d,C_9-Me), 1.4(3H,s,C_5-Me), 2.35(3H,s,NMe), 3.1(1H,d,C_1-H), 7.2-7.7(3H,m,Ar-H), 8.0(1H,m,C_4'-H).

Mass Spec. M/Z 229(M^+), 214($M^+ \div C_5$-Me),

84($CH_3-\underset{H}{\overset{|}{C}}=\underset{H}{\overset{|}{C}}-\overset{+}{N}\begin{matrix}CH_3\\ \diagdown\\ =CH_2\end{matrix}$) base peak.

Elemental analysis:

Found C, 78.3 ; H, 8.0 ; N, 6.1%

$C_{15}H_{14}NO$ requires C, 78.6 ; H, 8.3 ; N, 6.1%

2,5,9-trimethyl-3,4,8-trioxo-6,7-benzomorphan (impure, from ether).

ν_{max} 1730cm^{-1}, 1670cm^{-1}.

^{1}H nmr δ_{CDCl_3} 1.04(3H,d,C_9-Me), 1.67(3H,s,C_5-Me), 3.2(3H,s,NMe), 4.0(1H,d,C_1-H), 7.4-7.8(3H,m,Ar-H), 8.02(1H,m,C_4'-H).

Mass Spec. M/Z 257(M^+).

7.1.3 Attempted oxidation of 2,5-dimethyl-6,7-benzomorphan.

7.1.3.1 Cerium (IV) ammonium sulphate dihydrate.

A solution of cerium (IV) ammonium sulphate (25.0g, 40mM) in 3.5M-nitric acid (100ml) was added dropwise, with stirring, to a solution of 2,5-dimethyl-6,7-benzomorphan (2.0g, 10mM) in 3.5M-nitric acid (50ml). The solution was heated at 60^o for 10 hours, cooled, diluted with water (150ml) and basified with ammonia solution. Extraction with ether gave only starting material.

7.1.3.2 With chromyl acetate.

Concentrated sulphuric acid (2.0ml) was added

to a stirred cold solution of 2,5-dimethyl-6,7-benzomorphan (2.0g, 10mM) in acetic anhydride (10ml). When the mixture had cooled to 0°C, chromium trioxide (2.5g, 25mM) in acetic anhydride (12ml) was added slowly with stirring at such a rate that the temperature did not exceed 10°C. The resulting mixture was stirred for further 2 hours, poured on ice, basified with ammonia solution and extracted with ether (3x100ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give an oil (1.97g) which was shown to be a mixture (tlc). IR and PMR spectra of this crude product indicated the presence of 8,8-diacetyl-6,7-benzomorphan (107). The diacetate (107) was hydrolyzed by refluxing in conc. sulphuric acid (0.45ml) in 50% ethanol (10ml) for 30 minutes. The solution was cooled, basified with ammonia solution and extracted with dichloromethane to give 2,5-dimethyl-8-oxo-6,7-benzomorphan (7%).

7.1.3.3 Chromium trioxide in sulphuric acid.

Concentrated sulphuric acid (9ml) was added to sufficient ice to make up a 100ml solution. 2,5-Dimethyl-6,7-benzomorphan (2.0g, 10mM) was added to half of this solution which was then heated under reflux. Chromium trioxide (2.5g, 25mM) was added to the remainder and the resulting solution added dropwise to the stirred mixture heated under reflux. The mixture was cooled, basified with ammonia solution and extracted with ether (3 x 100ml). The ethereal extracts were washed with water, dried ($MgSO_4$) and

evaporated to give a yellow oil, which was distilled at 0.05mmHg. This was shown to consist of two major components (tlc). The IR and ^1H nmr of the mixture indicated it was mainly starting material and 2,5-dimethyl-8-oxo-6,7-benzomorphan (<20%).

7.1.3.4 Silver nitrate/ammonium persulphate.

A mixture of 2,5-dimethyl-6,7-benzomorphan (0.5g, 2.5mM), ammonium persulphate (1.5g,6.6mM) and silver nitrate (0.2g) was stirred in water for 3.5 hours at 60°C. The mixture was cooled, basified with ammonia solution and extracted with ether. The solvent was removed under vacuum leaving a oily residue which was identified as starting material with some impurity.

7.1.3.5 With 2,3-dichloro-5,6-dicyanobenzoquinone.

Dichlorodicyanobenzoquinone (1.04g, 4.6mM) was added, with stirring, to a solution of 2'hydroxy-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.3mM) in methanol (30ml) and the solution refluxed for 3 hours. The methanol was removed and the residue extracted with warm toluene (3 x 50ml). The toluene extracts were washed with water, dried ($MgSO_4$) and evaporated to give yellow solid. IR spectrum of the crude material did not show the presence of a carbonyl group. PMR spectrum indicated a mixture of starting material and 2'hydroxy-2,5-dimethyl-8α-methoxy-6,7-benzomorphan (113) in a 65:35 ratio.

2'hydroxy-2,5-dimethyl-8α-methoxy-6,7-benzomorphan (crude mixture).

^{1}H nmr δ_{CDCl_3} 1.83(3H,s,C_5-Me), 2.52(3H,s,NMe), 3.47(3H,s,$OC\underline{H}_3$), 4.24(1H,s,C_8-$\underline{H}$), 6.6-7.0(3H,m,Ar-$\underline{H}$), 8.70(1H,s,O$\underline{H}$, exchangeable).

Mass Spec M/Z 247(M^+).

7.2 Reactions of Ketones.

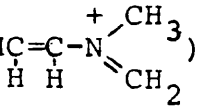
7.2.1 2,5-Dimethyl-8-oxo-6,7-benzomorphan oxime (117).

Method a.

A mixture of 2,5-dimethyl-8-oxo-6,7-benzomorphan (2.0g, 9.3mM), hydroxylamine hydrochloride (1.0g, 14.5mM) and sodium acetate trihydrate (2.1g, 15mM) in 95% ethanol was heated under reflux for 16 hours. The mixture was cooled, neutralized with aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 x 100ml). The dichloromethane extracts were washed with water (100ml), dried ($MgSO_4$) and evaporated to afford 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime (1.1g, 51%), mp 181-182^o (from chloroform).

^{1}H nmr δ_{DMSO} 1.35(3H,s,Me), 2.28(3H,s,NMe), 4.40(1H,t,C_1-$\underline{H}$), 7.0-7.4(3H,m, Ar-$\underline{H}$), 7.97(1H,dd,C_4'-$\underline{H}$), 11.33(1H,s,O$\underline{H}$, exchangeable).

Mass Spec. M/Z 230(M^+), 213(M^+÷OH) base peak,

70 ()

Elemental analysis:

Found C, 73.6 ; H, 7.8 ; N, 12.0%

$C_{14}H_{18}N_2O$ requires C, 73.0 ; H, 7.9 ; N, 12.2%

Method b.

A solution of hydroxylamine was prepared by mixing hydroxylamine hydrochloride (1.4g, 20mM) and sodium acetate (1.7g, 20mM) in 70ml ethanol. After 1 hour the mixture was filtered and the filtrate was treated with 2.8g (13mM) of 2,5-dimethyl-8-oxo-6,7-benzomorphan. After 8 hours of reflux the solution was concentrated to 20ml and upon cooling and filtering 1.8g (60%) oxime was obtained.

Analytical data same as those given for Method a.

7.2.2 2,5,9-Trimethyl-8-oxo-6,7-benzomorphan oxime (119).

A mixture of 2,5,9-trimethyl-8-oxo-6,7-benzomorphan (2.3g, 10mM), hydroxylamine hydrochloride (1.0g, 14.5mM) and sodium acetate trihydrate (2.1g, 15mM) in 95% ethanol was heated under reflux for 16 hours, and the procedure from 7.2.1 a. was repeated. The oxime was crystallized from chloroform, mp 188-189°. Yield 1.0g (41%).

^{1}H nmr δ_{DMSO} 0.72(3H,d,C_9-Me), 1.35(3H,s,C_5-Me), 2.28(3H,s,NMe), 4.24(1H,d,C_1-H), 7.0-7.4(3H,m,Ar-H), 8.0(1H,d,C_4'-H), 11.0(1H,s,N-OH, exchangeable).

Mass Spec. M/Z 244(M^+), 227(M^+÷OH)

84 ($CH_3C(H)=C(H)-\overset{+}{N}(Me)=CH_2$) base peak.

Elemental analysis:

Found C, 74.1 ; H, 8.0 ; N, 11.1%

$C_{15}H_{20}N_2O$ requires C, 73.7 ; H, 8.3 ; N, 11.5%

7.2.3 Beckmann Rearrangement of 8-oxo-2,5-dimethyl-6,7-benzomorphan oxime.

2,5-Dimethyl-8-oxo-6,7-benzomorphan oxime (1.0g, 4.3mM) in polyphosphoric acid (20g) was stirred at 150°C for 2 hours. The brown reaction mixture was cooled, poured into water and basified with ammonia solution. Extraction with dichloromethane and removal of solvent yielded a semi-solid residue, which was crystallized from ethyl acetate-petroleum ether to give 6,9-dimethyl-4,5-benzo-3,9-diazabicyclo [4.3.1] decen -2-one (0.6g, 40%), mp 169-72°.

ν_{max} (nujol) 1665cm^{-1} ($CO_{str.}$)

^{1}H nmr δ_{CDCl_3} 1.6(3H,s,Me), 2.55(3H,s,NMe), 9.5(1H,s,NH, exchangeable).

Mass Spec. M/Z 230(M^+).

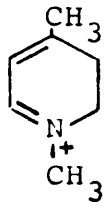
7.2.4 8α-Cyano-2,5-dimethyl-6,7-benzomorphan (121).

Potassium-t-butoxide (4.5g, 40mM) was added, all at once, to an ice-cooled solution of tosylmethyl isocyanide (3.0g, 15mM) in dry dimethyl sulphoxide (15ml). After stirring for 5 min. under nitrogen, methanol (0.25ml) was added and then 2,5-dimethyl-8-oxo-6,7-benzomorphan (1.0g, 4.6mM). The mixture was stirred

for 1 hour at room temperature under nitrogen and then for 70 hours at 45°C. The reaction mixture was diluted with water (200ml) and the solution extracted with hydrochloric acid (1N, 3 x 50ml). The combined acid extracts were washed with ether (100ml), basified with ammonia solution and extracted with ether (3 x 100ml). The ethereal extracts were dried ($MgSO_4$) and evaporated to give 8α-cyano-2,5-dimethyl-6,7-benzomorphan (0.8g, 76%) as a white solid, mp 101-102° (from acetone).

ν_{max} 2235cm^{-1} (CN).

^{1}H nmr δ_{CDCl_3} 1.4(3H,s,C_5-Me), 2.4(3H,s,NMe), 4.12(1H,s,C_8-H), 7.0-7.2(4H,m, Ar-H).

Mass Spec. M/Z 226(M^+), 211($M^+ \div C_5$-Me) base peak, 110( , dihydropyridine ion).

The hydrochloride was crystallized from ethanol and had mp 220-221°.

Elemental analysis:

Found C, 68.4 ; H, 7.3 ; N, 10.6%

$C_{15}H_{19}N_2Cl$ requires C, 68.8 ; H, 7.3 ; N, 10.7%

7.2.5 Attempted synthesis of 8β-cyano-2,5-dimethyl-6,7-benzomorphan by racemisation of the 8α-cyano-2,5-dimethyl-6,7-benzomorphan.

7.2.5.1 With potassium-t-butoxide.

The 8α-cyano-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.5mM) was added to a solution of potassium (0.2g, 5.0mM) in freshly distilled tertiary-butanol (100ml). The resulting mixture was stirred at room temperature for 3 hours, poured into ice water and extracted with dichloromethane (3 x 50ml). Removal of solvent under reduced pressure afforded 2,5-dimethyl-8-oxo-6,7-benzomorphan (0.5g, 95%),indistinguishable (IR, NMR, MS, GLPC) from authentic sample.

7.2.5.2 Sodium hydride.

A mixture of 2,5-dimethyl-8α-cyano-6,7-benzomorphan (0.5g, 2.5mM) and sodium hydride (0.12g, 5mM) in freshly distilled tetrahydrofuran was stirred at room temperature for 2 hours. The solution was cooled, treated with cold water (100ml) and extracted with dichloromethane. The solvent was removed under vacuum leaving a pale yellow oil which was identified (IR, NMR, MS, GLPC) to be 2,5-dimethyl-8-oxo-6,7-benzomorphan.

The procedure above was repeated under strict nitrogen atmosphere, and the reaction followed by thin layer chromatography. No 2,5-dimethyl-8-oxo-6,7-benzomorphan was detected for up to 4 hours suggesting the role played by atmospheric oxygen.

7.3 Primary Amines.

7.3.1 8α-Amino-2,5-dimethyl-6,7-benzomorphan (127).

a. Raney alloy (1.5g, 13mM) was added in small portions to a magnetically stirred solution of 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime (1.0g, 4.3mM) in ethanol (20ml) and sodium hydroxide (20ml). The mixture was stirred at ambient temperature for 5 hours and then filtered. The filtrate was extracted with dichloromethane (3 x 75ml), washed with water (50ml), dried ($MgSO_4$) and evaporated to give 8α-amino-2,5-dimethyl-6,7-benzomorphan as a colourless oil (0.65g, 69%).

ν_{max} 3425cm^{-1}, 3350cm^{-1}, 1603cm^{-1}.

^1H δ_{CDCl_3} 1.45(3H,s,C_5-Me), 1.56(2H,s,N$\underline{H}_2$, exchangeable), 2.42(3H,s,NMe), 2.87(1H,t,C_1-$\underline{H}$), 4.0(1H,s,C_8-$\underline{H}_\beta$), 7.0-7.4(4H,m,Ar-$\underline{H}$).

Mass Spec. M/Z 216(M^+), 184($M^+ \div C_5$-Me$\div$$NH_3$), 146($M^+ \div$70), 70($H\underset{H}{C} = \underset{H}{C} - \overset{+}{N}\begin{matrix} CH_3 \\ \diagdown\!\!\diagup \\ CH_2 \end{matrix}$) base peak.

The dioxalate was crystallized from ethanol and had mp 202-203°.

Elemental analysis:

Found C, 54.7 ; H, 5.5 ; N, 7.2%

$C_{18}H_{22}N_2O_8$ requires C, 54.8 ; H, 5.6 ; N, 7.1%

b. A mixture of the oxime (0.5g, 2.2mM) and platinum oxide (50mg, 0.2mM) in absolute ethanol (80ml) containing conc. hydrochloric acid (4ml) was hydrogenated at 50 psi in a rocking Parr apparatus at room temperature for 3 hours. The catalyst was removed by filtration and the filtrate evaporated to give a white solid which was dissloved in water (50ml). The solution was made basic with ammonia solution, extracted with dichloromethane (3 x 150ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded 8α-amino-2,5-dimethyl-6,7-benzomorphan as a colourless oil (0.34g, 72%).

Spectroscopic data were identical to those given for 7.3.1 a.

7.3.2 8β-Amino-2,5-dimethyl-6,7-benzomorphan (126).

2,5-Dimethyl-8-oxo-6,7-benzomorphan oxime (1.0g, 4.3mM) was added slowly, with stirring, to a mixture of lithium aluminium hydride (0.8g, 21mM) in dry ether (100ml) under nitrogen. The mixture was stirred overnight, cooled and water (3.2ml), sodium hydroxide (5N, 0.6ml) added dropwise with cooling and stirring. The solid was removed via filtration and repeatedly washed with ether. The organic phase was washed with water (50ml), dried ($MgSO_4$) and evaporated to give a colourless oil (0.60g, 64%).

ν_{max}	3475cm^{-1}, 3400cm^{-1}, 1603cm^{-1}
^{1}H nmr δ_{CDCl_3}	1.33(3H,s,Me), 2.40(2H,s,NH_2, exchangeable), 2.62(3H,s,NMe), 2.97(1H,m,

C_1-H, 4.0(1H,d,C_8-$\underline{H}_\alpha$;J=6Hz), 7.08-7.4(3H,m,Ar-$\underline{H}$), 7.6(1H,m,C_4'-$\underline{H}$), 0.9(1H,m,C_4-$\underline{H}$).

Mass spec. M/Z 216(M^+), 184($M^+ \div C_5$-Me$\div NH_3$), 146($M^+ \div 70$), 70($H\underset{H}{C} = \underset{H}{C}-\overset{+}{N}\overset{CH_3}{\underset{=CH_2}{}}$) base peak.

Treatment of the oil with ethereal HCl and crystallization afforded 8β-amino-2,5-dimethyl-6,7-benzomorphan dihydrochloride, mp 212-213°.

Elemental analysis:

Found C, 58.0 ; H, 7.5 ; N, 9.7%

$C_{14}H_{22}N_2Cl_2$ requires C, 58.1 ; H, 7.7 ; N, 9.7%

7.3.3 8α-Amino-2,5,9-trimethyl -6,7-benzomorphan (132).

The procedure described in 7.3.1a was repeated using 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime instead of 2,5-dimethyl-8-oxo-6,7-benzomorphan oxime to give 8α-amino-2,5,9-trimethyl-6,7-benzomorphan as an oil (60% yield).

ν_{max} 3400cm^{-1}, 3300cm^{-1}, 1603cm^{-1}.

^{1}H nmr δ_{CDCl_3} 0.96(3H,d,C_9-Me), 1.35(3H,s,C_5-Me), 1.90(2H,s,$N\underline{H}_2$, exchangeable), 2.45(3H,s,NMe), 2.88(1H,d,C_1-$\underline{H}$), 3.96(1H,s,C_8-$\underline{H}_\beta$), 7.0-7.6(4H,m,Ar-$\underline{H}$).

Mass spec. M/Z 230(M^+), 148($M^+ \div 84$), 84($\overset{CH_3}{\underset{H}{\diagdown}}C=\underset{H}{C}-\overset{+}{N}\overset{CH_3}{\underset{=CH_2}{}}$) base peak.

The oil was converted into its dioxalate salt and crystallized from ethanol, mp 180°.

Elemental analysis:

Found C, 60.1 ; H, 5.6 ; N, 7.0%

$C_{19}H_{24}N_2O_8$ requires C, 55.9 ; H, 5.9 ; N, 6.9%

7.3.4 Attempted synthesis of 8β-amino-2,5,9-trimethyl-6,7-benzomorphan (133).

A mixture of 2,5,9-trimethyl-8-oxo-6,7-benzomorphan oxime (0.5g, 2.0mM) and lithium aluminium hydride (0.4g, 10mM) was stirred in ether and the procedure described for 7.3.2 was repeated.

After removal of solvent (ether) under reduced pressure, the crude product was examined by ^1H and ^{13}C NMR, IR spectroscopy and mass spectrometry. Proton and carbon-13-nuclear magnetic resonance spectra indicated a mixture of 8α- and 8β-amino-2,5,9-trimethyl-6,7-benzomorphan in a 40:60 ratio. Attempts to isolate pure β-amine by fractional crystallization as hydrochloride, oxalate or hydrobromide from various solvent mixtures was unsuccessful.

ν_{max} 3400cm^{-1}, 3300cm^{-1}, 1603cm^{-1}.

^1H nmr δ_{CDCl_3} (of crude β-amine) 0.83(3H,d,C_9-Me), 1.35(3H,s,C_5-Me), 2.6(3H,s,NMe), 4.0(1H,d,C_8-H_α,J=6Hz), 7.0-7.78(4H,m,Ar-H)

Mass Spec. M/Z 230(M^+), 146(M^+÷84),

84() base peak.

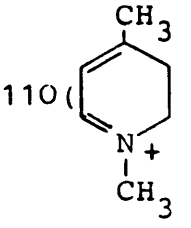
7.3.5 8α-Aminomethyl-2,5-dimethyl-6,7-benzomorphan (184).

8α-Cyano-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.2mM) was dissolved in absolute ethanol (50ml). Platinum oxide (50mg) and chloroform (2ml) were added to the solution and the mixture hydrogenated at 50 psi in a rocking Parr apparatus at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated to give a white solid. Recrystallization from ethanol afforded 8α-(aminomethyl)-6,7-benzomorphan dihydrochloride (0.54g, 81%) as needles, mp 260° (d).

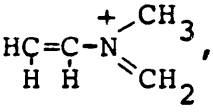
ν_{max} 3380cm^{-1}, 3320cm^{-1}, 760cm^{-1}.

^{1}H nmr δ_{CDCl_3} (free base) 1.36(3H,s,C_5-Me), 1.6(2H,s,NH_2,exchangeable), 2.40(3H,s,NMe), 2.6-3.0(3H, m,C_8-H + CH_2-NH_2), 3.13(1H,t,C_1-H; J=4Hz), 7.0-7.2(4H,m,Ar-H).

Mass Spec. M/Z 230(M^+), 200($M^+ \div CH_2NH_2$) base peak,



110( ),



70(, ion b)

Elemental analysis:

Found C, 59.6 ; H, 7.8 ; N, 9.3%

$C_{15}H_{24}N_2Cl_2$ requires C, 59.4 ; H, 8.0 ; N, 9.2%

7.3.6 Attempted synthesis of 8α-aminomethyl-6,7-benzomorphan by reduction of 8-cyanobenzomorphan.

7.3.6.1 With lithium aluminium hydride.

8α-Cyano-2,5-dimethyl-6,7-benzomorphan (1.0g, 4.4mM) in dry ether (100ml) was added dropwise, with stirring, to a mixture of lithium aluminium hydride (0.8g, 21mM) in dry ether (100ml). The resulting mixture was refluxed for 5 hours, cooled and water (2.8ml) and sodium hydroxide (5N; 0.6ml) added dropwise with cooling and stirring. The solid was removed by filtration and repeatedly washed with ether. The ether phase was washed with water (50ml), dried ($MgSO_4$) and evaporated in vacuo to give an oil. Thin layer chromatography showed four to five major components, two of which gave positive ninhydrin reaction. Two compounds, 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan and 8α-aldehyde of 2,5-dimethyl-6,7-benzomorphan, could be distinguished from spectroscopic analysis. The oil was chromatographed on silica gel column eluting with ethanol-dioxane-toluene-ammonia (10:40:45:5) and collecting 15ml fractions to give impure 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan (5%). Spectroscopic data were the same as those given for 7.3.5.

8α-formyl-2,5-dimethyl-6,7-benzomorphan:

ν_{max} 1675cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} (crude aldehyde) 1.32(3H,s,Me), 2.5(3H,s,NMe), 3.1(1H,

t,C_1-H;J=4Hz), 4.7(1H,m,C_8-H), 7.1-7.4(4H,m,Ar-H).

7.3.6.2 With mixture of lithium aluminium hydride and aluminium chloride.

A mixture of 8α-cyano-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.2mM), lithium aluminium hydride (0.2g, 4.4mM) and aluminium chloride (0.4g, 5.2mM) in dry ether was stirred for 2 hours. The usual lithium aluminium hydride work up gave an oil which showed a complex mixture on analysis by TLC. PMR and IR spectra were similar to those of the products obtained from lithium aluminium hydride reduction (7.3.6.1). The reaction mixture was not examined further.

7.4 Amides.

7.4.1 8α-Acetamido-2,5-dimethyl-6,7-benzomorphan (134).

Acetyl chloride (0.30ml, 4.2mM) was added dropwise, with stirring, to a solution of 8α-amino-2,5-dimethyl-6,7-benzomorphan (0.50g, 2.3mM) and triethylamine (1.0ml) in dry ether (100ml). The solution was stirred for 6 hours, washed with water (2 x 50ml) and extracted with hydrochloric acid (0.5N, 2 x 50ml). The acid extracts were basified with ammonia solution and extracted with ether (3 x 100ml).

The ethereal phase was washed with water (50ml), dried ($MgSO_4$) and evaporated to give 8α-acetamido-6,7-benzomorphan as a white solid (0.42g, 70%).

ν_{max} (nujol)	3300cm^{-1} (NH), 1640cm^{-1} ($CO_{str.}$).
^1H nmr δ_{CDCl_3}	1.40(3H,s,C$\underline{H}_3$), 1.92(3H,s,CO-C$\underline{H}_3$), 2.60(3H,s,NMe), 3.04(1H,t,C_1-$\underline{H}$), 5.2(1H,d,C_8-$\underline{H}$;J with NH =8Hz on D_2O d→s), 5.9(1H,d,N$\underline{H}$), 7.0-7.4(4H,m,Ar-$\underline{H}$).
Mass Spec. M/Z	258(M^+), 243(M^+÷C_5-Me), 199(M^+÷NH_2-$COCH_3$), 110(dihydropyridine ion), 70(ion b) base peak.

The hydrochloride was crystallized from ethanol and had mp. 212-213°.

Elemental analysis:

Found	C, 64.8	; H, 7.8	; N, 9.2%
$C_{16}H_{21}N_2OCl$ requires	C, 65.2	; H, 7.9	; N, 9.5%

7.4.2 8α-Cyclopropionamido-2,5-dimethyl-6,7-benzomorphan (138).

To a solution of 8α-amino-2,5-dimethyl-6,7-benzomorphan (1.1g, 5.1mM) in a mixture of dichloromethane (100ml) and triethylamine (3.5ml) was added cyclopropane carboxylic acid chloride (1.3g, 15mM). The mixture was refluxed for 12 hours and evaporated. The oily residue was dissolved in ether (200ml), washed with water (2 x 75ml) and extracted with hydrochloric acid (0.5N, 3 x 50ml). The aqueous layer was basified with ammonia solution and extracted

with dichloromethane (3 x 100ml). The dichloromethane layer was washed with water (50ml), dried ($MgSO_4$) and evaporated to give 8α-cyclopropionamido-2,5-dimethyl-6,7-benzomorphan as a white amorphous solid (0.9g, 62%). Recrystallization from ethyl acetate/petroleum ether gave the 8α-cyclopropionamide as white needles, mp. 205°.

ν_{max} (nujol) 3295cm^{-1} (NH), 1670cm^{-1} ($CO_{str.}$).

^1H nmr δ_{CDCl_3} 1.4(3H,s,C_5-Me), 0.6-1.36(4H,m,CO-c-$C_3\underline{H}_5$), 2.56(3H,s,NMe), 3.06(1H, t,C_1-$\underline{H}$;J=4Hz), 5.2(1H,d,C_8-$\underline{H}$;J=10Hz on D_2O d⟶s), 6.1(1H,d,N$\underline{H}$;J=10Hz; exchangeable), 7.1-7.4(4H,m,Ar-$\underline{H}$).

Mass Spec. M/Z 284(M^+), 249($M^+ \div C_5$-Me), 225($M^+ \div 59$), 184($M^+ \div C_5$-Me$\div NH_2CO$-c-C_3H_5), 110(dihydropyridine ion), 70(ion b) base peak, 59($CH_3CH_2\overset{+}{N}HCH_3$).

Elemental analysis:

Found C, 75.7 ; H, 8.5 ; N, 9.5%

$C_{18}H_{24}N_2O$ requires C, 76.0 ; H, 8.5 ; N, 9.8%

7.4.3 8α-Phenylacetamido-2,5-dimethyl-6,7-benzomorphan (136).

Phenylacetyl chloride (0.5ml, 3.8mM) was added dropwise to a stirred suspension of 8α-amino-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.3mM) in a mixture of potassium carbonate (0.5g, 3.6mM) and methanol

(25ml) and water (3ml). The mixture was stirred for 4 hours and evaporated. The residue was dissolved in ether (200ml), washed with water (3 x 50ml) and extracted with hydrochloric acid (0.3N, 3 x 50ml). The acid extracts were basified with ammonia solution and extracted with dichloromethane (3 x 100ml). The dichloromethane phase was washed with water, dried ($MgSO_4$) and evaporated to give 8α-phenylacetamido-2,5-dimethyl-6,7-benzomorphan (0.55, 71%) as colourless plates, mp. 172-173° (from ethanol-ether).

ν_{max} (Nujol)	3290cm^{-1} (NH), 1630cm^{-1} CO$_{(str.)}$.
^{1}H nmr δ_{CDCl_3}	1.36(3H,s,C_5-Me), 2.6(3H,s,NMe), 3.06(1H,t,C_1-H;J=4Hz), 3.5(2H, s,-COCH_2Ph), 5.16(1H,d,C_8-H$_\beta$;J=8Hz; on D_2O d→s), 5.7(1H,d,NH;exchangeable), 7.0-7.4(9H,m,Ar-H).
Mass Spec. M/Z	334(M^+), 319(M^+÷C_5-Me), 275(M^+÷59), 184(M^+÷C_5-Me÷NH_2COCH_2Ph), 110(dihydropyridine ion), 70(ion b) base peak.

Elemental analysis:

Found	C, 78.9	; H, 8.0	; N, 8.2%
$C_{22}H_{26}N_2O$ requires	C, 79.0	; H, 7.8	; N, 8.4%

7.4.4 8α-Chloroacetamido-2,5-dimethyl-6,7-benzomorphan (163).

Chloroacetyl chloride (0.75ml, 9.4mM) was added dropwise with a microlitre syringe, with stirring, to

a cold solution of 8α-amino-2,5-dimethyl-6,7-benzomorphan (0.5g, 2.3mM) and triethylamine (1ml) in dry acetone (50ml). The mixture was stirred at 0^{o} for 3 hours, filtered and the filtrate was evaporated. The residue was dissolved in ether (100ml) and extracted with hydrochloric acid (0.25N, 3 x 50ml). The aqueous layer was washed with ether (30ml), basified with ammonia solution and extracted with dichloromethane. The dichloromethane layer was dried ($MgSO_4$) and evaporated to afford a white amorphous substance. Recrystallization from ethyl-acetate gave 8α-chloroacetamido-2,5-dimethyl-6,7-benzomorphan (0.42g, 63%) as colourless needles, mp 214^{o} (d).

ν_{max} 3350cm^{-1}, 1660cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} 1.4(3H,s,C_5-Me), 2.6(3H,s,NMe), 3.08(1H,t,C_1-H), 4.0(2H,s,-$COCH_2Cl$), 5.2(1H,d,C_8-H;J=10Hz, on D_2O d→s), 6.6(1H,d,NH;J=10Hz,exchangeable), 7.08-7.4(4H,m,Ar-H).

Mass Spec. M/Z 292(M^+), 277($M^+ \div C_5$-Me), 256($M^+ \div Cl$), 199($M^+ \div NH_2COCH_2Cl$), 110(dihydropyridine ion), 70(ion b) base peak.

Elemental analysis:

Found C, 66.0 ; H, 7.5 ; N, 9.6%

$C_{16}H_{21}N_2OCl$ requires: C, 65.6 ; H, 7.2 ; N, 9.6%

7.4.5 8β-Acetamido-2,5-dimethyl-6,7-benzomorphan (135).

8β-Amino-2,5-dimethyl-6,7-benzomorphan was acylated by the same procedure as described in 7.4.1 to afford 8β-acetamido-2,5-dimethyl-6,7-benzomorphan as an oil in 68% yield. The hydrochloride recrystallized from ethanol had mp 229-230°.

ν_{max}	3345cm^{-1} (NH), 1660cm^{-1} ($CO_{str.}$).
^{1}H nmr δ_{CDCl_3} (base)	0.9(1H,m,C_4-H), 1.37(3H,s,C_5Me), 2.14(3H,s,$COCH_3$), 2.62(3H,s,NMe), 5.3(1H,dd,C_8-H_α;J=6Hz,10Hz, on D_2O dd→d), 7.0-7.35(3H,m,Ar-H), 7.4(1H,m,C_4'-H).
Mass Spec. M/Z	258(M^+), 243(M^+÷Me), 199(M^+÷NH_2COCH_3), 110, 70 base peak.

Elemental analysis:

Found	C, 61.5	; H, 7.8	; N, 8.9%
$C_{16}H_{23}N_2OCl\cdot H_2O$ requires	C, 61.0	% H, 8.0	; N, 8.9%

7.4.6 8β-Dicyclopropionamido-2,5-dimethyl-6,7-benzomorphan (140).

The procedure described in section 7.4.2 was repeated using 8β-amino-2,5-dimethyl-6,7-benzomorphan to give 8β-dicyclopropionamido-2,5-dimethyl-6,7-benzomorphan as an oil (67%).

ν_{max} (Nujol)	3300cm^{-1}, 1712cm^{-1}, 1660cm^{-1}, 1642cm^{-1}, 1380cm^{-1}.

^{1}H nmr δ_{CDCl_3} 0.7-1.2(8H,m,2(c-C_3H_5)), 1.32(3H,s,C_5-Me), 2.52(3H,s,NMe), 3.04(1H,m, C_1-H), 6.08(1H,d,C_8-H_α;J~6Hz), 6.9-7.3(4H,m,Ar-H).

Mass Spec. M/Z 352(M^+), 283(M^+÷CO-c-C_3H_5), 226, 198(283÷NH_2CO-c-C_3H_5) base peak, 184 (M^+÷C_5-Me-NH(CO-c-C_3H_5)$_2$), 110, 70.

The hydrochloride was crystallized from isopropanol and had mp 141°.

Elemental analysis:

Found C, 67.5 ; H, 7.7 ; N, 6.9%

$C_{22}H_{28}N_2O_2$·HCl requires C, 67.9 ; H, 7.5 ; N, 7.2%

7.4.7 8β-Phenylacetamido-2,5-dimethyl-6,7-benzomorphan (137).

In the manner described in 7.4.3 acylation of 8β-amino-2,5-dimethyl-6,7-benzomorphan (1.0g, 4.6mM) gave 1.07g (69%) of an amorphous white solid. This crystallized from ethyl acetate as colourless needles, mp 78°.

ν_{max} 3330cm^{-1} (NH), 1640cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} 1.32(3H,s,C_5-Me), 2.62(3H,s,NMe), 2.90(1H,m,C_1-H), 3.68(2H,s,PhCH_2CO), 5.17(1H,dd,C_8-H;J~6Hz, 8Hz, on D_2O dd→d), 7.0-7.42(10H,m,Ar-H + NH reduced to 9H on D_2O).

Mass Spec. M/Z 334(M^+), 319, 275(M^+÷59), 184,

91($PhCH_2^+$), 70 base peak.

Elemental analysis:

Found C, 79.1 ; H, 8.0 ; N, 8.3%

$C_{22}H_{26}N_2O$ requires: C, 79.0 ; H, 7.8 ; N, 8.4%

7.4.8 8β-Chloroacetamido-2,5-dimethyl-6,7-benzomorphan (162).

By the same method as described in 7.4.4, 8β-amino-2,5-dimethyl-6,7-benzomorphan (1.0g) afforded 8β-chloroacetamido-2,5-dimethyl-6,7-benzomorphan as an oil (0.72g, 53%).

ν_{max} 3330cm^{-1} (NH), 1670cm^{-1} ($CO_{str.}$).

^1H nmr δ_{CDCl_3} 1.37(3H,s,C_5-Me), 2.6(3H,s,NMe), 3.04(1H,m,C_1-H), 4.15(2H,s,$COCH_2Cl$), 5.2(1H,dd,C_8-H;J with C_1-H=6Hz,J with NH=10Hz, on D_2O dd→d), 7.0-7.25(3H,m, Ar-H), 7.3(1H,m,C_4'-H), 8.05(1H,d,NH, exchangeable), 0.96(1H,m,C_4-H).

Mass Spec. M/Z 294(M^+), 199($M^+ \div NH_2COCH_2Cl$), 70 base peak.

The hydrochloride recrystallized as colourless prisms, mp. 206-208°, from ethanol.

Elemental analysis:

Found C, 55.7 ; H, 6.8 ; N, 7.9%

$C_{16}H_{22}N_2OCl_2 \cdot H_2O$ requires C, 55.3 ; H, 7.0 ; N, 8.1%

7.4.9 2,8-Bridged-6,7-benzomorphan derivative (165).

A cold solution of 8β-chloroacetamido-2,5-dimethyl-6,7-benzomorphan (0.10g, 0.34mM) in dry acetone (5ml) was added slowly to a stirred ice cold solution of sodium iodide (0.065g, 0.4mM) in dry acetone (10ml). The mixture was stirred at ambient temperature for 2 hours and the sodium chloride precipitate was filtered off. The filtrate was evaporated to give a white solid. Recrystallization from ethanol afforded 2,8-bridged cyclic quaternary salt (0.09g, 51%), mp. 240°.

^{1}H nmr δ_{DMSO_4} 1.47(3H,s,C_5-Me), 3.32(3H,s,$\overset{+}{N}$Me), 3.42(2H,s,$COC\underline{H}_2\overset{+}{N}$), 4.30(3H,m,$C_1$-H + C_3-H), 5.16(1H,d,C_8-H;J~6Hz), 7.1-7.3(3H,m,Ar-H), 7.68(1H,m,C_4'-H), 9.84(1H,m,NH).

Mass Spec. M/Z 256(M^+÷127), 242, 59 base peak.

Elemental analysis:

Found C, 49.7 ; H, 5.7 ; N, 7.2%

$C_{16}H_{21}N_2OI$ requires C, 50.0 ; H, 5.5 ; N, 7.3%

7.4.10 8α-(Acetamidomethyl)-2,5-dimethyl-6,7-benzomorphan (187).

8α-(Aminomethyl)-2,5-dimethyl-6,7-benzomorphan (0.8g, 3.4mM) was acetylated by the same procedure as described in section 7.4.1 to afford 8α-(acetamidomethyl)-2,5-dimethyl-6,7-benzomorphan as an oil

(0.67g, 71%). The hydrochloride crystallized as colourless plates from ethanol, mp. 228-229°.

ν_{max} 3350cm^{-1}(NH), 1660cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} (base) 1.38(3H,s,C_5-Me), 2.04(3H,s,$COC\underline{H}_3$), 2.37(3H,s,NMe), 3.0(1H,t,C_1-$\underline{H}$; J~4Hz), 3.05-3.6(3H,m,C_8-$\underline{H}$ + $C\underline{H}_2NH$) 6.44(1H,m,N$\underline{H}$, exchangeable), 7.0-7.5(4H,m,Ar-$\underline{H}$).

Mass Spec. M/Z 272(M^+), 257(M^+÷Me), 213(M^+÷NH_2COCH_3), 110 base peak.

Elemental analysis:

Found C, 74.4 ; H, 9.3 ; N, 10.4%

$C_{17}H_{24}N_2O$ requires C, 75.0 ; H, 8.9 ; N, 10.3%

7.4.11 8α-(Cyclopropionamidomethyl)-2,5-dimethyl-6,7-benzomorphan (188).

8α-(Cyclopropionamidomethyl)-2,5-dimethyl-6,7-benzomorphan (63%) was prepared from 8α-(aminomethyl)-2,5-dimethyl-6,7-benzomorphan by the same procedure as described in 7.4.2.

ν_{max} 3350cm^{-1} (NH), 1665cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} (base) 0.8-1.1(4H,m,c-$C_3\underline{H}_5$), 1.40(3H,s,C_5-Me), 2.36(3H,s,NMe), 3.0(1H,t,C_1-$\underline{H}$;J~4Hz), 3.04-3.8(3H,m,$C\underline{H}C\underline{H}_2NH$), 6.36(1H,m, N$\underline{H}$, exchangeable), 7.0-7.5(4H,m,Ar-$\underline{H}$).

Mass Spec. M/Z 298(M^+), 283(M^+÷Me), 200(M^+÷CH_2NHCO-c-C_3H_5), 199(M^+÷C_5-Me÷NH_2CO-c-C_3H_5).

100, 70, 69($CO\text{-}c\text{-}C_3H_5^+$) base peak.

The hydrochloride was recrystallized from ethanol-ether and had mp. 209°.

Elemental analysis:

Found	C, 65.0	; H, 8.3	; N, 7.6%
$C_{19}H_{27}N_2OCl \cdot H_2O$ requires	C, 64,6	; H, 8.3	; N, 7.9%

7.4.12 8α-(Phenylacetamidomethyl)-2,5-dimethyl-6,7-benzomorphan (189).

The procedure described in section 7.4.3 was repeated using 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan to give 8α-(phenylacetamidomethyl)-2,5-dimethyl-6,7-benzomorphan (81%) as white solid. Recrystallization from ether gave colourless plates, mp. 110-111°.

ν_{max} (Nujol)	3360cm^{-1}, 1642cm^{-1} ($CO_{str.}$).
^1H nmr δ_{CDCl_3}	1.34(3H,s,C_5-Me), 2.18(3H,s,NMe), 2.77(1H,t,C_1-H;J~4Hz), 2.90-3.53(3H,m,C_8-H + CH_2NH), 3.56(2H,s,$PhCH_2CO$), 6.0(1H,d,NH), 7.0-7.4(9H,m,Ar-H).
Mass Spec. M/Z	348(M^+), 333(M^+-Me), 198(M^+-Me-$NHCOCH_2Ph$), 110 base peak, 91($PhCH_2^+$), 70.

Elemental analysis:

Found	C, 79.2	; H, 8.2	; N, 8.0%
$C_{23}H_{28}N_2O$ requires	C, 79.3	; H, 8.1	; N, 8.0%

7.4.13 8α-(Chloroacetamidomethyl)-2,5-dimethyl-6,7-benzomorphan (164).

The procedure described in section 7.4.4 was repeated using 8α-aminomethyl-2,5-dimethyl-6,7-benzomorphan instead of 8α-amino-2,5-dimethyl-6,7-benzomorphan to give 8α-(chloroacetamidomethyl)-2,5-dimethyl-6,7-benzomorphan (53%) as an oil.
The hydrochloride was recrystallized from ethanol, and had mp. 212° (d).

ν_{max}	3350cm^{-1} (NH), 1660cm^{-1} ($CO_{str.}$).
^{1}H nmr δ_{CDCl_3} (base)	1.40(3H,s,C_5-Me), 2.36(3H,s,NMe), 2.95(1H,t,C_1-H), 3.08-3.80(3H,m, C_8HCH_2NH), 4.7(2H,s,CH_2Cl), 6.84(1H,m,NH,exchangeable), 7.0-7.5(4H, m,Ar-H).
Mass Spec. M/Z	306(M^+), 291(M^+÷Me), 110 base peak, 70.

Elemental analysis:

Found	C, 59.4	; H, 7.4	; N, 7.9%
$C_{17}H_{24}N_2OCl_2$ requires	C, 59.5	; H, 7.1	; N, 8.2%

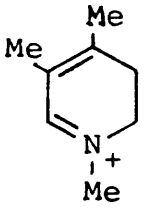
7.4.14 8α-Acetamido-2,5,9-trimethyl-6,7-benzomorphan (145).

8α-Acetamido-2,5,9-trimethyl-6,7-benzomorphan was obtained in 58% yield from 8α-amino-2,5,9-trimethyl 6,7-benzomorphan by the same procedure as that described in section 7.4.1. The hydrochloride was crystallized

from ethanol-ether and had mp. 203°.

ν_{max} 3300cm^{-1} (NH), 1640cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} (base) 0.92(3H,d,C_9-Me), 1.4(3H,s,C_5-Me), 2.0(3H,s,$COCH_3$), 2.6(3H,s,NMe), 2.95(1H,d,C_1-H;J~8Hz), 5.25(1H,d, C_8-H_B;J~10Hz, on D_2O d→s), 5.8(1H, d,NH;J~10Hz, D_2O exchangeable), 7.0-7.4(4H,s,Ar-H).

Mass Spec. M/Z 272(M^+), 257(M^+÷Me), 213(M^+÷NH_2COCH_3), 124(), 84 base peak.

Elemental analysis:

Found C, 64.6 ; H, 8.6 ; N, 9.2%

$C_{17}H_{22}N_2O\cdot HCl$ requires C, 65.1 ; H, 8.2 ; N, 9.1%

7.4.15 8α-Cyclopropionamido-2,5,9-trimethyl-6,7-benzomorphan (146).

8α-Amino-2,5,9-trimethyl-6,7-benzomorphan was acylated in the same manner as described in section 7.4.2 to give 8α-cyclopropionamido-2,5,9-trimethyl-6,7-benzomorphan in 61% yield (from ethyl acetate-petroleum ether).

ν_{max} 3295cm^{-1} (NH), 1670cm^{-1} ($CO_{str.}$).

^{1}H nmr δ_{CDCl_3} 0.6-1.1(7H,m,CO-c-C_3H_5 & C_9-Me), 1.4(3H,s,C_5-Me), 2.6(3H,s,NMe), 2.96(1H,d,C_1-H;J~7Hz), 5.28(1H,d,

C_8-$\underline{H}_\beta$; J~10Hz, on D_2O d→s), 5.85(1H, d, N$\underline{H}$; J~10Hz), 7.0-7.4(4H, 's', Ar-$\underline{H}$).

Mass Spec. M/Z 298(M^+), 283(M^+÷Me), 198(M^+÷Me÷NH_2CO-c-C_3H_5), 84 base peak.

Elemental analysis:

Found C, 76.2 ; H, 9.0 ; N, 9.3%

$C_{19}H_{26}N_2O$ requires C, 76.5 ; H, 8.8 ; N, 9.4%

7.4.16 8α-Phenylacetamido-2,5,9-trimethyl-6,7-benzomorphan (147).

This compound was prepared in 64% yield from 8α-amino-2,5,9-trimethyl-6,7-benzomorphan by the same procedure as that described in section 7.4.3. The amide was crystallized from ethyl acetate-ether to give white crystals, mp. 136°.

ν_{max} 3290cm^{-1}, 1630cm^{-1} ($CO_{str.}$).

^1H nmr δ_{CDCl_3} 0.9(3H,d,C_9-Me), 1.30(3H,s,C_5-Me), 2.6(3H,s,NMe), 2.8(1H,d,C_1-$\underline{H}$; J~8Hz), 3.6(2H,s,$COC\underline{H}_2Ph$), 5.2(1H,d,C_8-$\underline{H}_\beta$; J~10Hz, on D_2O d→s), 5.6(1H,d,N$\underline{H}$; J~10Hz, exchangeable), 7.0-7.5(9H, m, Ar-$\underline{H}$).

Mass Spec. M/Z 348(M^+), 333(M^+÷Me), 289(M^+÷59), 198(M^+÷Me÷NH_2COCH_2Ph), 84 base peak.

Elemental analysis:

Found C, 79.2 ; H, 8.0 ; N, 8.0%

$C_{23}H_{28}N_2O$ requires C, 79.3 ; H, 8.1 ; N, 8.0%

7.5 Secondary amines.

7.5.1 Attempt to synthesis alkylamines. Reductive alkamination of 2,5-dimethyl-8-oxo-6,7-benzomorphan with sodium cyanohydridoborate.

To a solution of anhydrous methylamine (2.3g, 7.2mM) in absolute methanol (25ml) was added 5N HCl-methanol (4.8ml), followed by 2,5-dimethyl-8-oxo-6,7-benzomorphan (2.6g, 12mM) and sodium cyanohydridoborate (450mg,7.1mM). The solution was stirred at 40^{o} for 72 hours. Concentrated hydrochloric acid was added until pH was 2, and the methanol removed *in vacuo*. The residue was taken up in water (50ml) and extracted with ether (2 x 30ml). The aqueous layer was basified with ammonia solution and extracted with dichloromethane (3 x 50ml). The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was chromatographed on silica gel using varying strengths of methanol-chloroform (1-10%) to give starting material, 8β-methylamino-2,5-dimethyl-6,7-benzomorphan (149, 8%) and 8β-hydroxy-2,5-dimethyl-6,7-benzomorphan (150, 14%). Attempts to improve the yield of the amine and reduce the undesired product by modifying the reaction conditions, eg. varying the reaction time, temperature and the time of addition of sodium cyanohydridoborate, met with limited success.

8β-hydroxy-2,5-dimethyl-6,7-benzomorphan, mp. 89-91^{o} (from acetone). (Lit. mp 88-90^{o}).

ν_{max} 3350cm^{-1}.

^{1}H nmr δ_{CDCl_3} 1.32(3H,s,C_5-Me), 2.58(3H,s,NMe), 3.90(1H,s,O<u>H</u>,exchangeable), 4.70(1H,d,C<u>H</u>OH;J~6Hz), 7.1-7.4(4H,m,Ar-<u>H</u>).

8<u>β</u>-methylamino-2,5-dimethyl-6,7-benzomorphan (impure).

ν_{max} 3350cm^{-1}, 1603cm^{-1}

^{1}H nmr $\delta_{CDCl_3,60Hz}$ 1.33(3H,s,C_5-Me), 2.05(1H,s,N<u>H</u>, exchangeable), 2.53(3H,s,NMe), 2.60(3H,s,N<u>H</u>Me), 3.2(1H,m,C_1-<u>H</u>), 3.65(1H,d,C_8-<u>H</u>;J~6Hz), 7.0-7.35(3H, m,Ar-<u>H</u>), 7.7(1H,m,Ar-<u>H</u>).

Mass Spec. M/Z 230(M^+).

7.5.2 <u>Alkylation of primary amines.</u>

<u>General procedure.</u>

Amides were prepared as in section 7.4 by treating the appropriate acyl halide (20mM) with the primary amines (10mM) in the presence of base (10mM). A solution of the crude amide in freshly distilled tetrahydrofuran (50ml) was added dropwise with stirring during 20 min., at room temperature, to a suspension of LAH (30mM) in tetrahydrofuran or ether (100ml). After the addition was completed the solution was refluxed for 5-8 hours, cooled in an ice bath and water (4.2ml), 5N sodium hydroxide (0.75ml) added dropwise with caution. The solid was removed by filtration and repeatedly washed with ether. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The resulting syrup was

taken up in ether and converted to the hydrochloride with ethereal-HCl. The hydrochloride was recrystallized from ethanol-ether or isopropanol-ether and yields varied from 15% to 45%.

7.5.2.1 8α-Ethylamino-2,5-dimethyl-6,7-benzomorphan (153).

Yield	36%
mp.	261° (from isopropanol)
ν_{max}	3320cm^{-1} (NH).
^{1}H nmr δ_{CDCl_3} (free base)	1.04-1.3(3H,t,$CH_2C\underline{H}_3$;J 8-10Hz), 1.4(3H,s,C_5-Me), 2.5(3H,s,NMe), 2.7-3.0(2H,q,$C\underline{H}_2CH_3$), 3.08(1H,t, C_1-$\underline{H}$), 3.87(1H,s,C_8-$\underline{H}_\beta$), 7.0-7.45(4H,m,Ar-$\underline{H}$).
Mass Spec. M/Z	244(M^+), 201(M^+÷Me÷CH_2=CH_2), 184(M^+÷Me÷NH_2Et), 59(EtNHMe) base peak.

Elemental analysis:

Found	C, 54.5 ; H, 8.3 ; N, 7.9%
$C_{16}H_{26}N_2Cl_2\cdot 2H_2O$ requires	C, 54.4 ; H, 8.6 ; N, 7.9%

7.5.2.2 8α-Cyclopropylmethylamino-2,5-dimethyl-6,7-benzomorphan (155).

Yield	43%
mp.	208-209° (from ethanol-ether).
ν_{max}	3300cm^{-1} (NH).

^{1}H nmr δ_{CDCl_3} (free base): 0-1.14(5H,m,c-C_3H_5), 1.4(3H,s,C_5-Me), 2.5(3H,s,NMe), 2.68(2H,d,NHC$\underline{H}_2$-c-C_3H_5;J~7Hz), 3.05(1H,t,C_1-$\underline{H}$;J~4Hz), 3.8(1H,s,C_8-$\underline{H}_\beta$), 7.1-7.5(4H, m ,Ar-$\underline{H}$).

Mass Spec. M/Z: 270(M^+), 213(M^+÷Me÷c-C_3H_6), 200(M^+÷Me÷CH_2-c-C_3H_5), 184(M^+÷Me÷NH_2CH_2-c-C_3H_5), 70, 59 base peak.

Elemental analysis:

Found: C, 62.8 ; H, 8.4 ; N, 8.2%

$C_{18}N_{26}N_2 \cdot 2HCl$ requires: C, 63.0 ; H, 8.2 ; N, 8.2%

7.5.2.3 8α-Phenylethylamino-2,5-dimethyl-6,7-benzomorphan (157).

Yield: 23%

mp.: 186-187° (from isopropanol-ether)

ν_{max}: 3368cm^{-1} (NH).

^{1}H nmr δ_{CDCl_3} (free base): 1.34(3H,s,Me), 2.47(3H,s,NMe), 2.7-3.3(5H,m,PhC$\underline{H}_2$C$\underline{H}_2$ and C_1-$\underline{H}$), 3.73(1H,s,C_8-$\underline{H}_\beta$), 6.8-7.6(10H,m, Ar-$\underline{H}$ + N$\underline{H}$).

Mass Spec. M/Z: 320(M^+), 201(M^+÷Me÷$PhCH_2CH$), 184(M^+÷Me÷$PhCH_2CH_2NH_2$), 59 base peak.

Elemental analysis:

Found: C, 65.3 ; H, 7.8 ; N, 7.0%

$C_{22}H_{30}N_2Cl_2 \cdot H_2O$ requires: C, 64.9 ; H, 7.8 ; N, 6.8%

7.5.2.4 8β-Ethylamino-2,5-dimethyl-6,7-benzomorphan (154).

Yield	38%
mp.	254-255° (from isopropanol-ether).
ν_{max}	3300cm^{-1} (NH).
^{1}H nmr δ_{CDCl_3} (free base)	0.8-1.05(1H,m,C_4-H), 1.1-1.3(3H,t, $CH_2\underline{CH_3}$), 1.4(3H,s,C_5-Me), 2.3(1H,s,NH, exchangeable), 2.6(3H,s,NMe), 2.68-3.04(2H,m,$C\underline{H_2}CH_3$), 3.17(1H,m, C_1-H), 3.74(1H,d,$C_8\underline{H}_\alpha$;J~6Hz), 7.0-7.4(3H, m ,Ar-H), 7.75(1H,m,C_4'-H).
Mass Spec. M/Z	244(M^+), 201, 184, 131, 59 base peak.

Elemental analysis:

Found	C, 60.4 ; H, 8.5 ; N, 8.8%
$C_{16}H_{26}N_2Cl_2$ requires	C, 60.6 ; H, 8.3 ; N, 8.8%

7.5.2.5 8β-Cyclopropylmethylamino-2,5-dimethyl-6,7-benzomorphan (156).

Yield	40%
mp.	188-189° (from ethanol-ether).
ν_{max}	3300cm^{-1} (NH).
^{1}H nmr δ_{CDCl_3} (free base)	0-1.1(6H,m,c-$C_3\underline{H_5}$ and C_4-H), 1.35(3H,s,Me), 2.6(3H,s,NMe), 2.68(2H,m, $C\underline{H_2}$-c-C_3H_5), 3.12(1H,m,C_1-H), 3.76(1H,d,C_8-H;J~6Hz), 7.0-7.4(3H,m,Ar-H), 7.76(1H,m,C_4'-H).

Mass Spec. M/Z 270(M^+), 213, 184, 70, 59 base peak.

Elemental Analysis:

Found C, 63.4 ; H, 7.9 ; N, 8.4%

$C_{18}H_{28}N_2Cl_2$ require C, 63.0 ; H, 8.2 ; N, 8.2%

7.5.2.6 8β-Phenylethylamino-2,5-dimethyl-6,7-benzomorphan (158).

Yield 18%

mp. 171-173° (from ethanol-ether).

ν_{max} 3300cm^{-1} (NH).

^1H nmr δ_{CDCl_3} (free base) 0.8(1H,m,C_4-H), 1.33(3H,s,C_5-Me), 2.55(3H,s,NMe), 2.8-3.4(5H,m, $PhCH_2CH_2$ + C_1-H), 3.75(1H,d,C_8-H_α; J~6Hz), 7.0-7.5(8H,m,Ar-H), 7.7(1H, m,C_4'-H).

Mass Spec. M/Z 320(M^+), 201, 184, 131, 59 base peak.

Elemental analysis:

Found C, 64.9 ; H, 7.9 ; N, 6.8%

$C_{22}H_{30}N_2Cl_2 \cdot H_2O$ requires C, 64.9 ; H, 7.8 ; N, 6.8%

7.5.2.7 8α-(Ethylaminomethyl)-2,5-dimethyl-6,7-benzomorphan (193).

Yield 28%

mp. 274° (from isopropanol-ether).

ν_{max} 3350cm^{-1} (NH).

^{1}H nmr δ_{CDCl_3} (free base)	1.04-1.24(3H,t,$CH_2\underline{CH_3}$;J~8Hz), 1.37(3H,s,Me), 2.40(3H,s,NMe), 2.4-3.25(6H,m,$\underline{CH_2}NHC\underline{H_2}$,$C_1$-$\underline{H}$ + C_8-$\underline{H_\beta}$), 7.0-7.4(4H,m,Ar-$\underline{H}$).
Mass Spec. M/Z	258(M^+), 201($M^+ \div CH_2{=}NCH_2CH_3$) 186(201÷Me)., 58 base peak.

Elemental analysis:

Found	C, 61.2	; H, 8.5	; N, 8.0%
$C_{17}H_{28}N_2Cl_2$ requires	C, 61.7	; H, 8.5	; N, 8.5%

7.5.2.8 <u>8α-(Cyclopropylmethylaminomethyl)-2,5-dimethyl-6,7-benzomorphan (194).</u>

Yield	31%
mp	238° (from isopropanol-ether).
ν_{max}	3340cm^{-1} (NH).
^{1}H nmr δ_{CDCl_3} (free base)	0.0-1.1(5H,m,c-$C_3\underline{H_5}$), 1.38(3H,s,C_5-Me), 2.4(3H,s,NMe), 2.46-3.3(6H,m,$C\underline{H_2}NH$ $C\underline{H_2}$,C_8-$\underline{H}$ + C_1-$\underline{H}$), 7.0-7.4(4H,m, Ar-$\underline{H}$).
Mass Spec. M/Z	284(M^+), 201, 84 base peak, 59.

Elemental analysis:

Found	C, 63.3	; H, 8.6	: N, 7.5%
$C_{19}H_{30}N_2Cl_2$ requires	C, 63.9	; H, 8.5	; N, 7.8%

7.5.2.9 8α-(Phenylethylaminomethyl)-2,5-dimethyl-6,7-benzomorphan (195).

Yield	16%
mp.	235-236° (from ethanol-ether).
ν_{max}	3340cm^{-1} (NH).
^{1}H nmr δ_{CDCl_3} (free base)	1.4(3H,s,Me), 2.4(3H,s,NMe), 2.4-3.3(8H,m,$C\underline{H}_2NHC\underline{H}_2C\underline{H}_2Ph$,$C_8$-$\underline{H}$ + C_1-$\underline{H}$), 7.0-7.5(9H,m,Ar-$\underline{H}$).
Mass Spec. M/Z	334(M^+), 201, 134 base peak, 59.

Elemental analysis:

Found	C, 66.3	; H, 7.9	; N, 6.6%
$C_{23}H_{32}N_2Cl_2$ requires	C, 67.8	; H, 7.9	; N, 6.9%

7.5.2.10 8α-Ethylamino-2,5,9-trimethyl-6,7-benzomorphan (159).

Yield	42%
mp	204° (from ethanol-ether).
ν_{max}	3320cm^{-1}.
^{1}H nmr δ_{CDCl_3} (free base)	0.84(3H,d,C_9-Me), 1.05(3H,t,$CH_2C\underline{H}_3$; J~8Hz), 1.3(3H,s,C_5-Me), 2.4(3H,s, NMe), 2.6-3.1(3H,m,$C\underline{H}_2CH_3$ and C_1-$\underline{H}$), 3.6(1H,s,C_8-$\underline{H}_B$), 7.0-7.3(3H,m,Ar-$\underline{H}$), 7.4(1H,m,C_4'-$\underline{H}$).
Mass Spec. M/Z	258(M^+), 198($M^+ \div C_5$-Me$\div NH_2CH_2CH_3$), 84, 59 base peak.

Elemental analysis:

Found C, 61.2 ; H, 8.1 ; N, 8.4%

$C_{17}H_{28}N_2Cl_2$ requires C, 61.6 ; H, 8.5 ; N, 8.5%

7.5.2.11 8α-Cyclopropylmethylamino-2,5,9-trimethyl-6,7-benzomorphan (160).

Yield 39%

mp. 192° (d)(from ethanol ether).

ν_{max} 3300cm^{-1} (NH).

^{1}H nmr δ_{CDCl_3} (free base) 0.0-0.8(5H,m,c-C_3H_5), 0.90(3H,d, C_9-Me), 1.32(3H,s,C_5-Me), 2.4(3H, s,NMe), 2.8(1H,d,C_1-H;J=7Hz), 3.6(1H,s,C_8-H$_\beta$), 7.0-7.3(3H,m,Ar-H), 7.4(1H,m,C_4'-H).

Mass Spec. M/Z 284(M^+), 227(M^+÷Me÷c-C_3H_6),198(M^+÷ C_5-Me÷NH_2CH_2-c-C_3H_5), 84, 59 base peak.

Elemental analysis:

Found C, 65.5 ; H, 8.1 ; N, 7.5%

$C_{19}H_{30}N_2Cl_2$ requires C, 63.8 ; H, 8.5 ; N, 7.8%

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